

JUNE

1959

VOL. XIX

NO. 6

# Circulation

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION



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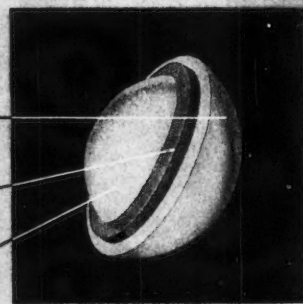
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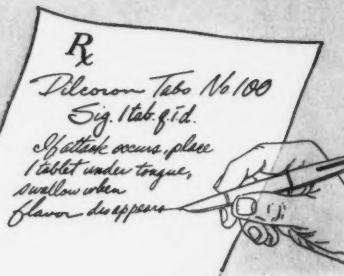
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# CIRCULATION

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Subscription rates, \$14.00 per year within the United States and Canada; \$15.00 per year elsewhere. Single copies, \$2.00; foreign, \$2.50. A combination subscription with *Circulation Research* is available at \$21.00 per year within the United States and Canada, \$23.00 per year elsewhere. Subscriptions are accepted on a calendar year basis.

Agents for Great Britain, H. K. Lewis & Co., Ltd., 136 Gower Street, London, W.C.1, England.

Published monthly at the Publication Office, 120 N. Green St., Chicago, Ill. Second class postage paid at Chicago, Ill.

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## Editorial

### Role of Connective Tissue Ground Substance in Degenerative Disease

THE widespread interest in the relationship between lipids and arteriosclerosis has largely obscured the relatively limited studies of the nature of tissue changes occurring in degenerative diseases. Recently, there has been an increased interest in the consideration of the possible role of mucopolysaccharides in vascular degeneration. For the most part this has been limited to an application of a few histochemical techniques of limited specificity. Frequently, these studies have not been interpreted critically in light of modern knowledge regarding the chemistry and physical chemistry of the acid mucopolysaccharides.

Several concepts lacking in experimental validation have been widely used in interpretation of histochemical changes. Among these has been the assumption that the observation of increased metachromatic staining is indicative of depolymerization of mucopolysaccharides. Whereas changes in molecular size of mucopolysaccharides may occur, changes in degree of metachromasia may depend upon many other factors.

Recent studies indicate that in cartilage chondroitinsulfuric acid-A is bound to protein by a firm linkage that appears to be covalent in nature. Chondroitinsulfuric acid-A chains of molecular weight of 50,000 are bound to a protein core to give a macromolecule with a minimum molecular weight of 4,000,000. On the basis of experience in attempting to isolate sulfated mucopolysaccharides from other tissues, it seems likely that these are also bound to proteins. Other studies indicate that hy-

aluronic acid is also bound to protein, although less firmly.

Another assumption that seems unreasonable on the basis of available chemical information is the release of serum mucoproteins by the depolymerization of acid mucopolysaccharides. This has resulted to some extent from a confusion of nomenclature. The acid mucopolysaccharides are linear polyelectrolytes composed of alternating units of a N-acetyl amino sugar and a uronic acid. Certain of the compounds are sulfated. As already indicated, certain of the acid mucopolysaccharides are associated with protein. Such mucopolysaccharide-protein complexes have sometimes been named mucoproteins. The same name has been used for a different class of chemical compounds which contain N-acetylglucosamine, galactose, mannose, and sialic tightly bound to protein. Such mucoproteins have been characterized in blood but it has so far been impossible to isolate any large molecular carbohydrate fraction free of protein from these substances. It seems unlikely, on chemical grounds, that the blood mucoproteins arise from the depolymerization of acid mucopolysaccharides of connective tissues. The transformation of acid mucopolysaccharides to mucoproteins would require a complete degradation of the molecule and the change of structure of most of the hexose components. The fact that serum mucoproteins (glycoproteins) are elevated in disease which show connective tissue changes in no way proves the causal relationship of the two phenomena. Indeed, the serum mucoproteins are elevated

in a wide variety of disease processes. This change is paralleled by a large number of other blood protein changes. The mechanism by which these changes occur in disease is not yet understood.

Recent chemical studies indicate that it is unwise to consider ground substance changes as a uniform phenomenon. At least 8 different acid mucopolysaccharides have now been isolated from connective tissues. These differ with respect to chemical composition and biological properties. The exact structure of some of these compounds is not yet known. It is apparent that there is specific localization of individual compounds. Table 1 lists the known compounds.

The mucopolysaccharide composition of the ground substance varies in specific tissues. Thus, most cartilage contains chondroitinsulfuric acid-A while skin contains a mixture of chondroitinsulfuric acid-B and a smaller amount of chondroitinsulfuric acid-A mixed with hyaluronic acid. The exact localization of individual polysaccharides in tissues is not yet known. They may play highly specific roles which depend upon both their anatomic localization and their biological activities. An example of the biological specificity is indicated by the fact that chondroitinsulfuric acid-B, which differs from chondroitinsulfuric acid-A only in the position of the OH group on C-5 of the uronic acid fraction, is antithrombic while chondroitinsulfuric acid-A has no activity on the coagulation system. This example is indicative of the many possibilities

TABLE 1.—*Acid Polymucosaccharides Isolated from Connective Tissue*

| Compound                    | Uronic acid     | Amino sugar   | Sulfate | Acetyl |
|-----------------------------|-----------------|---------------|---------|--------|
| Hyaluronic acid             | Glucuronic acid | Glucosamine   | —       | +      |
| Chondroitin-sulfuric acid-A | Glucuronic acid | Galaetosamine | +       | +      |
| Chondroitin-sulfuric acid-B | Iduronic acid   | Galaetosamine | +       | +      |
| Chondroitin-sulfuric acid-C | Glucuronic acid | Galaetosamine | +       | +      |
| Chondroitin                 | Glucuronic acid | Galaetosamine | —       | +      |
| Keratosulfate               | (Galaetose)     | Glucosamine   | +       | +      |
| Heparin                     | Glucuronic acid | Glucosamine   | +       | —      |
| Heparin monosulfuric acid   | Glucuronic acid | Glucosamine   | +       | +      |

that specific localization or changes of individual compounds may result in profound physiologic and pathologic alterations.

This brief discussion is intended to focus attention on possibilities for the study of connective tissue changes in vascular degenerative disease but to warn against too ready acceptance of concepts that are not firmly based on critical evidence.

ALBERT DORFMAN



## THE PHYSICIAN

HIPPOCRATES

Greek physician, about 460-377 B.C.

For where there is love of man, there is also love of the art. For some patients, though conscious that their condition is perilous, recover their health simply through their contentment with the goodness of the physician.—*Precepts*. Trans. W. H. S. Jones. From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources*. Vol. I, Boston, The Beacon Press, 1952.

# A Clinical Study of 1,000 Consecutive Cases of Mitral Stenosis Two to Nine Years after Mitral Valvuloplasty

By LAURENCE B. ELLIS, M.D., DWIGHT E. HARKEN, M.D., AND  
HARRISON BLACK, M.D.

A study is presented of 1,000 cases of predominant mitral stenosis operated by valvuloplasty between 1949 and 1956. It is shown that the survival of these patients is better than would have been expected under medical management. Sixty-nine per cent of the survivors of the operation in groups II and III improved, and 55 per cent in group IV. Factors influencing the late results are discussed. After substantial improvement lasting a year or more, 228 of this series deteriorated; the factors affecting this deterioration are discussed, of which mitral insufficiency, an inadequate valvuloplasty, and recurrent rheumatic fever are the most striking.

THE present study is a report of the clinical results in 1,000 consecutive cases with a preoperative diagnosis of predominant mitral stenosis on whom mitral valvuloplasty was performed between the years 1949 and March 1956. Ninety-two per cent of the operations were performed by D.E.H. and the remainder by H.B. The follow-up of all of these patients has been carried out under the direction of the cardiologist, L.B.E., who has had the final word in the preoperative classification of the patients and in the estimate of the degree of improvement that they have had. In 150 (table 1) mitral insufficiency of some degree was suspected before operation; 121 showed evidence of aortic stenosis or insufficiency but this was not thought to be clinically important, and there were 6 who were believed to have tricuspid stenosis. No attempt was made to classify patients with tricuspid insufficiency,

which was presumably due in most cases to functional dilatation of the annulus in patients with a failing right ventricle. Patients in whom the preoperative diagnosis of significant mitral stenosis was in doubt or who had very substantial amounts of associated valvular disease, in whom exploratory cardiomyotomies were carried out, are not included in the present series and will be the subject of a separate report. No patient has been dropped from the series, even if the operative findings did not confirm the preoperative diagnosis.

The technique of operation has been described elsewhere.<sup>1, 2</sup> The basic principles of the valvuloplastic procedure have remained unchanged throughout the series, although with increasing experience the correction of stenosis has undoubtedly been improved. An initial group of 11 patients operated on between the years of 1947 and 1949 by techniques not strictly comparable to the present one have not been included.

The results in the first 500 patients in this series followed for a shorter period of time and a preliminary statement of some of the results of the entire group of 1,000 have been previously published.<sup>3-6</sup>

The classification employed<sup>1</sup> roughly corresponds to the functional classification of the New York Heart Association, but it is designed to represent a more dynamic picture

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This material was presented in part at the Third World Congress of Cardiology, Brussels, September 1958.

The study was supported by grant no. 442 of the National Heart Institute, U. S. Public Health Service. Physical facilities were generously provided by the Boston Mutual Life Insurance Company.

of the course of the patient's illness. This series included no patients in group I, that is patients without significant symptoms. Nineteen were in group II; these were patients somewhat handicapped by symptoms from their disease but who were able to carry on a sedentary occupation successfully and in whom the condition was not progressive. In 4 of these patients who did not have severe symptoms of cardiac disability the primary indication for operation was one or more peripheral emboli. Group III included patients suffering mainly from pulmonary symptoms, which were usually progressive in nature and were sufficiently handicapped, so that ordinary activities were significantly limited. If these patients had had overt congestive failure, it had been because of some unusual precipitating cause such as pregnancy or a serious infection and they had rapidly recovered from it. There were 711 in this group. Group IV comprised cardiac patients with more severe symptoms who were mostly cardiac invalids suffering from chronic congestive failure or who were maintained in a precarious state of compensation only by vigorous medical means. There were 270 in this group.

In 58 of the patients included in this series, a second operation was performed by us for mitral stenosis and in 1 patient 3 operations were done. We originally operated on 49 of these patients, and in 10 the operation had been previously performed elsewhere. In these patients the clinical evidence prior to the second operation pointed toward significant mitral stenosis and the operation was performed with a view toward carrying out a mitral valvuloplasty. Five patients in this series have had a second operation for mitral stenosis performed by other surgeons. Five have been reoperated on by us for mitral insufficiency, and in 5 an exploratory cardiectomy has been performed. In 2 a second operation for the correction of aortic stenosis has been carried out. This series includes 17 patients who have been counted twice and 1 who was counted 3 times. Hence, the number 1,000 refers to the number of operations rather than the number of

patients. In the remaining 41 who were reoperated on, only 1 operation is included in this series, the other being done either before or after this series of 1,000 or was carried out elsewhere.

Twenty-one patients were operated on while they were pregnant and there were 3 deaths among them. Although this represents a special group, in a consideration of operative mortality, pregnancy does not alter the late results. In the follow-up studies these patients have been included with the others. The place of mitral surgery during pregnancy has been discussed elsewhere.<sup>7</sup>

Females outnumbered males in this series about 3 to 1, 78 per cent of the patients in group III being women and 74 per cent of the group IV patients. The average age of the patients in the series was 39.4 years (38.8 years for women and 40.5 years for men) (table 3).

#### *Accuracy of the Preoperative Diagnosis of Mitral Stenosis and Mitral Insufficiency Judged by Findings at Operation*

A preoperative diagnosis of mitral insufficiency complicating mitral stenosis was not made unless it was considered to be clinically significant. This would correspond to the finding of a moderate or marked mitral insufficiency by the surgeon at operation. We have, therefore, compared the preoperative diagnosis with the operative finding at operation. When the preoperative diagnosis was pure mitral stenosis the findings were confirmed at operation in the group III patients in 84 per cent of those in atrial fibrillation and 94 per cent of patients in normal sinus rhythm, and in group IV patients in 83 and 75 per cent respectively. However, if a preoperative diagnosis of mitral stenosis and insufficiency was made, in only 56 per cent of the patients in both groups was the diagnosis of moderate to severe insufficiency confirmed at operation. If the situation is considered from the opposite point of view, the findings are similar. When pure mitral stenosis was found at operation the lesion had been correctly diagnosed pre-

TABLE 1.—*Preoperative Diagnosis*

|                                  | Group II and III |                                   | Group IV        |                                   | Total |
|----------------------------------|------------------|-----------------------------------|-----------------|-----------------------------------|-------|
|                                  | Mitral stenosis  | Mitral stenosis and insufficiency | Mitral stenosis | Mitral stenosis and insufficiency |       |
| Without associated heart lesions | 556              | 73                                | 186             | 48                                | 863   |
| With aortic valvular disease     | 77               | 19                                | 21              | 4                                 | 121   |
| With tricuspid stenosis          | 1                | 1                                 | 0               | 4                                 | 6     |
| With coronary disease            | 3                | 0                                 | 6               | 1                                 | 10    |
| Totals                           | 637              | 93                                | 213             | 57                                | 1000  |

operatively in 94 per cent of the group III patients and 84 per cent in the group IV patients, whereas when significant mitral insufficiency was found by the surgeon at operation a correct diagnosis had been made prior to operation in 42 per cent of group III and 52 per cent of group IV patients.

One of the patients who had been classed in group III preoperatively had a valve that appeared normal at operation. In all, 15 group III patients were found to have valves of 2.0 cm.<sup>2</sup> or more, prior to valvuloplasty; of these 6 had some degree of mitral insufficiency. In 3 of these 15 the chief indication for surgery was a history of emboli. In 25 more the preoperative valve size was from 1.5 to 1.9 cm.<sup>2</sup>; and 18 of these had mitral insufficiency.

Two patients in group IV had normal mitral valves; 1 had a large atrial thrombus overlying the valve, and in the other the heart failure was presumably due to coronary atherosclerosis. Two other patients in group IV had valve orifices of 2.0 cm.<sup>2</sup> or more, and in 3 the preoperative valve size was from 1.5 to 1.9 cm.<sup>2</sup> In all 5 of these patients substantial mitral insufficiency was present.

#### OPERATIVE MORTALITY

The over-all operative mortality for this group has been previously reported and is given in table 2. Because of the very small

TABLE 2.—*Effect of Experience on Operation Mortality*

| Serial no. of patients | Groups II and III |               | Group IV |               |
|------------------------|-------------------|---------------|----------|---------------|
|                        | Number            | Mortality (%) | Number   | Mortality (%) |
| 1-100                  | 59                | 14            | 41       | 32            |
| 101-500                | 296               | 4             | 104      | 24            |
| 501-1000               | 375               | 0.8           | 125      | 19            |

number of group-II patients in this series these have been included with group-III patients in the subsequent analyses, and whenever the expression "group III" is used, it denotes group II and III patients. There was 1 operative death in the group-II patients. For the purpose of this analysis "operative mortality" denotes death during the operation or during the period of the hospitalization when the operation was performed.

The operative mortality according to age is given in table 3, and it will be seen that there is no significant change in operative mortality depending upon age. It is a matter of interest that none of the 42 patients over 50 in group III died an operative death.

The operative mortality for males in group III was 2.5 per cent and for females it was 3.3 per cent. Among the group-IV patients the mortality was somewhat higher in the male group, being 29.6 per cent as compared to 21.6 in the females but this difference is not significant since the *p* value is between 0.05 and 0.10.\* These figures are for the entire 1,000 cases. Actually, the operative mortality has fallen strikingly in the second 500 cases, particularly in group-III patients (table 2).

#### PERIPHERAL EMBOLIZATION

One hundred eighty-six of the 1,000 patients had had one or more well-documented attacks of peripheral embolization prior to surgery. The time of onset of these episodes varied from many years before surgery to a few days. The risk of developing an operative embolus in the last 500 patients operated upon was

\*Unless otherwise noted, *p* values shown here and in the ensuing discussion are based on a contingency  $\chi^2$  test.<sup>8</sup> Values of *p* less than .05 are significant.

TABLE 3.—Operative Mortality by Age

| Age by decades | Groups II and III |               | Group IV          |               |
|----------------|-------------------|---------------|-------------------|---------------|
|                | No. of operations | Mortality (%) | No. of operations | Mortality (%) |
| 10-19          | 6                 | 0.0           | —                 | —             |
| 20-29          | 120               | 3.3           | 7                 | 28.6          |
| 30-39          | 290               | 3.4           | 55                | 23.6          |
| 40-49          | 272               | 3.3           | 118               | 20.2          |
| 50-59          | 40                | 0.0           | 79                | 29.2          |
| 60-69          | 2                 | 0.0           | 11                | 18.2          |
| Total          | 730               | 3.1           | 270               | 23.6          |

2.1 per cent in group III and 8.0 per cent in group IV (table 4). The higher rate of operative embolization in the first 500 patients has been discussed elsewhere.<sup>3</sup> The figures for the second 500 reflect more accurately our current experience. Only 1 of the 8 emboli in group III was fatal, but 8 of the 10 in group IV had a fatal outcome. Although the number of emboli occurring in fibrillating patients was higher than in patients with normal rhythm, the differences are not statistically significant. The frequency of embolization in patients with normal rhythm is of interest.

Of the entire group of 913 patients who survived operation 25 have developed one or more peripheral emboli after the operative period to July 1, 1958. Most of the patients who developed late peripheral emboli were fibrillating at the time of surgery and were presumably fibrillating at the time of embolization. A few who were in normal rhythm at the time of surgery were known to have developed fibrillation prior to the occurrence of their late emboli. No relationship, however, could be ascertained between the occurrence of late emboli and emboli occurring at operation or a history of embolization occurring prior to surgery. The average duration of time since operation in this group is almost exactly 4 years and this therefore represents an experience of about 3,600 patient years or an embolization rate of 0.7 per cent per year in this group. More than half of the surviving patients were in chronic atrial fibrillation. It is

TABLE 4.—Operative Embolization in Relation to Rhythm in the Second Five Hundred Patients of the Series

| Occurrence of operative emboli | Groups II and III |                         |                            | Group IV        |                         |                            |
|--------------------------------|-------------------|-------------------------|----------------------------|-----------------|-------------------------|----------------------------|
|                                | No. of patients   | No. of embolic episodes | Per cent with embolization | No. of patients | No. of embolic episodes | Per cent with embolization |
| Total operative emboli         |                   |                         |                            |                 |                         |                            |
| Normal sinus rhythm            | 211               | 4                       | 1.9                        | 27              | 1                       | 3.7                        |
| Atrial fibrillation            | 164               | 4                       | 2.4                        | 98              | 9                       | 9.1                        |
| Total                          | 375               | 8                       | 2.1                        | 125             | 10                      | 8.0                        |

our opinion that valvuloplasty confers substantial protection against peripheral embolization in patients of this type.

#### SURVIVAL

In spite of the great number of studies that have been made over the years on the survival of patients with mitral stenosis it is extremely difficult to obtain data on medically treated patients that are comparable to this series. Many studies are statistically invalid or are made on groups that are not easily comparable, or consider only the survival period of those who ultimately were known to be dead. Most studies based on autopsy statistics are retrospective, so that it is almost impossible to determine when and to what degree the patients became symptomatic. A recent study has been reported by Wilson and Lim<sup>9</sup> on the survival of patients followed into the third, fourth, and fifth decades of life from the onset of rheumatic fever in childhood. Although this is an important study, it is difficult to compare it with our own. Elsewhere we have commented<sup>5</sup> on the studies made by Grant,<sup>10</sup> Wilson and Greenwood,<sup>12</sup> and Hamilton and Thompson.<sup>11</sup> Vedoya, Nessi, and Mendelzon<sup>13</sup> have also reported the ominous prognosis of patients with symptomatic mitral stenosis. Recently, Rowe et al.<sup>14</sup> found that 40 per cent of 250 patients with mitral stenosis followed 10 years were dead, and Donzelot et

al.<sup>15</sup> have published results that have indicated that surgically treated patients have a better prognosis than those medically followed. So far as these studies are comparable to ours, they indicate that survival under medical therapy is less than for our surgically treated patients.

As we have previously indicated,<sup>5</sup> the series most comparable to ours which has been medically treated and followed is that by Olesen,<sup>16</sup> who studied a group of patients first observed between the years of 1933 and 1949 in Copenhagen. In this series 72 per cent of the patients were females as compared to 77 per cent in our group and the average age of his patients was 41.5 years as compared to 39.4 years in our series. He classified his patients according to the grouping of the American Heart Association and also subdivided the class-2 and class-3 patients into those who were fibrillating and those in normal sinus rhythm. Our group-III patients would most closely approximate his class-3 patients and class-2 patients with atrial fibrillation, and our group-IV patients are comparable to his class-4 patients. We have therefore utilized his data to compare our group-III patients with his male and female patients in class 3 and class 2 in atrial fibrillation. Figures 1 and 2 show the survival of our patients compared to Olesen's groups. Patients who have been re-operated on and are counted twice in the series are counted only once in the calculation of the survival curves.\* It will be seen that, including an operative mortality of 3 per cent, 83 per cent of our group-III patients have survived over the period of observation up to 7 years, and 71 per cent to 9 years, although the numbers dealt with in the last 2 years are small. This survival is better than for the medically treated patients. In group IV 57 per cent have survived up to 9 years, which include an operative mortality of 24 per cent or the group as a whole. This survival is astly better than for the medically treated

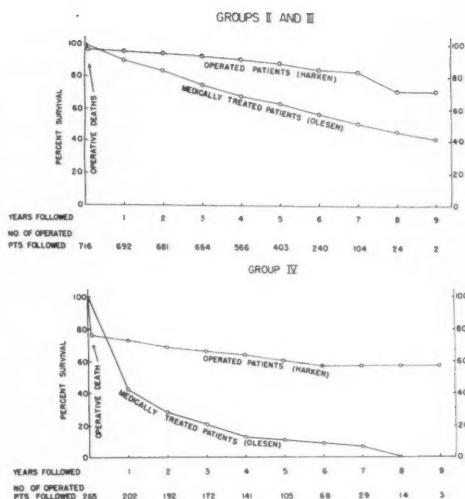


FIG. 1 Top. Survival rates. A comparison of operated with medically treated patients.

FIG. 2 Bottom. Survival rates. A comparison of operated with medically treated patients.

patients of whom none was alive at 8 years.

The survival rates have also been analyzed according to age, sex, and rhythm. Total survival curves for each of these classes are not shown in detail. The survival rates of patients at the end of 5 years are shown in table 5.

The survival of female patients is somewhat better than of males; those in normal rhythm do better than fibrillating patients; and younger patients in group III survive longer than do those who are older. The only one of the differences, however, which is statistically significant is the sex difference in group III ( $p < .01$ ).

#### LATE DEATHS

Ninety-five patients have died since operation. The causes of the deaths are given in table 6. Eleven died of conditions clearly unrelated to their heart disease. Two of these, however, were patients in which death might be considered related to the operative procedure, including 1 death 21½ months following surgery from hepatitis, which might have been homologous serum jaundice acquired from a transfusion at the time of surgery, and

\*The survival curves were calculated according to the method of Berkson et al.<sup>17</sup>

TABLE 5.—*Survival Rates of Patients at the End of Five Years in Relation to Age, Sex, and Rhythm*

|                     | Groups II and III                                      |               | Group IV   |               |
|---------------------|--|---------------|--|---------------|
|                     | No. of patients observed at start of fifth year period | Survival rate | No. of patients observed at start of fifth year period | Survival rate |
| Sex                 |  |               |  |               |
| Male                | 91   | 80            | 26   | 54            |
| Female              | 312  | 90            | 79   | 63            |
| Rhythm              |  |               |  |               |
| Normal sinus        | 242  | 90            | 26   | 65            |
| Atrial fibrillation | 161  | 85            | 79   | 60            |
| Age by decades      |  |               |  |               |
| 10-19               | 4  | 83            | —  | —             |
| 20-29               | 73   | 95            | 3  | 43            |
| 30-39               | 176  | 91            | 28   | 60            |
| 40-49               | 134  | 87            | 49   | 65            |
| 50-59               | 15   | 64            | 21   | 60            |
| 60-69               | 1  | 100           | 4  | 54            |

1 death from a reaction occurring during the course of an intercostal block for treatment of residual intercostal pain. There were 4 sudden deaths that have been assumed to be cardiac in origin. Patients developing cerebral vascular accidents, whether fatal or not, following surgery have been considered to have had these on the basis of emboli dislodged from the heart, though some of these may have been due to independent vascular disease of the brain. In the calculation of the survival curves all deaths have been included, whether or not they were of cardiac origin.

#### FOLLOW-UP STUDIES

##### *Follow-up Procedure*

Nine hundred thirteen patients survived operation. All but 2 have been followed for at least 1 year or more, up to July 1, 1958, at which point the analyses were made. Of the patients followed for at least 1 year, 1 has been lost to follow-up for 5 years, 3 for 4 years, 1 for 3 years, and 8 for 2 years. Ninety-three have been delinquent in follow-up less than 2 years, but most of these patients are merely overdue in their annual follow-up question-

TABLE 6.—*Causes of Late Deaths*

| Diagnosis                   | Number of deaths |
|-----------------------------|------------------|
| Primarily cardiac           | 76               |
| Heart failure               | 60               |
| Sudden                      | 4                |
| Peripheral emboli           | 9                |
| Pulmonary infarcts          | 2                |
| Pneumonia and heart failure | 1                |
| Noncardiac                  | 11               |
| Unknown                     | 8                |
| Total                       | 95               |

naire by 1 or 2 months. In addition the 48 patients who have had a second cardiac operation have been dropped from the series as unimproved at that point and hence are technically "lost to follow-up." All of the remainder have been followed up to the latest anniversary of their operation. All patients have been followed by annual questionnaires so worded as to obtain not only the subjective opinion of the patient concerning his improvement but to provide evidence from which an estimate can be made as to whether the patient is capable of carrying on with less disability than he had prior to operation. In addition all other obtainable data concerning these patients have been utilized. These include personal examinations of a large number of these patients, letters from doctors, hospital reports, and so forth. In a previously reported study<sup>18</sup> a comparison has been made of the accuracy of method of follow-up with a follow-up examination made personally by one of us on a sample of 101 patients from this group. It was found that the grading of patients by the questionnaire method was stricter and somewhat lower than the grading of patients by personal examination. The final estimate of the degree of improvement of each of the patients has been made by one of us on the basis of all the information obtainable. Very often this is less than the subjective opinion of the patient himself. Some patients, of course, have proved to be difficult to evaluate, particularly when they have had other diseases or noncardiac

symptoms. This is especially true of many patients with neurotic symptoms, and of patients handicapped by the residua of vascular accidents occurring either before or during surgery. Patients who have been partially incapacitated by vascular accidents occurring at the time of surgery have been graded in accordance with the handicap they have suffered from the neurologic residua of their emboli irrespective of the cardiac status.

#### CRITERIA OF IMPROVEMENT

Patients have been classed as markedly improved, moderately improved, slightly improved, unchanged, and worse. *Markedly improved* patients are those who have gone up 2 grades in the American Heart Association classification or the few group-II patients who have lost all their symptoms. Thus patients who were originally in group III are considered markedly improved if they are now in class 1 of the American Heart Association classification, and for the group-IV patients an improvement into class 1 or 2 of the American Heart Association classification would justify a grading of markedly improved. *Moderately improved* patients are those who have improved 1 grade in the American Heart Association classification. For the sake of the analysis in the following discussion patients who are *moderately to markedly improved* have been classed together as "*significantly improved*" or as "*improved*"; those who are only *slightly improved, unchanged, worse, or dead* are considered as "*unimproved.*"

#### CUMULATIVE IMPROVEMENT

Figure 3 shows the improvement of the patients at each year of follow-up. This improvement is calculated on the basis of the follow-up of each patient at each anniversary of his operation for the total period of follow-up. In a few patients where there has been a hiatus of more than 1 year between 2 follow-up reports, the state of improvement reported at the first follow-up has been considered to have been maintained to the year preceding the next time that information is available by

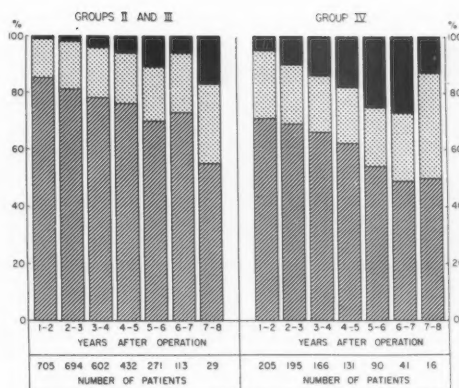


FIG. 3. Status of operated patients at each year of follow-up. *Solid*, dead; *Spotted*, unimproved; *Lined*, improved.

a follow-up report, unless it is clear from the information on the last follow-up just when any change in status occurred.

The improvement in both groups III and IV has tended to drop somewhat with succeeding years of follow-up. To some extent this may be due to the obvious fact that those patients who have been followed for the longest time are also those who were operated on early in our experience with this operation, and the operative attack on the valve may have been less adequate at that time. While the quality of surgery undoubtedly improved progressively in this series no fundamental changes in technical principles were made until early in the second thousand operations. The tendency for the improvement to become less over the years represents at least in part the inevitable ravages of the disease process. Residual damage to the cardiac muscle, pulmonary vasculature, liver, and so forth may have persisted and left its effect, particularly in the group-IV patients. In addition, other factors which may be present are an operative fracture which was less than adequate; restenosis; mitral insufficiency; associated valvular disease, and recurrent rheumatic activity. A more detailed analysis will be made later in this report of the factors affecting the deterioration of patients who previously have been significantly improved.

TABLE 7.—*Status of 911 Patients at Last Follow-up*

| Degree of improvement | Groups II and III |                               | Group IV        |                               |
|-----------------------|-------------------|-------------------------------|-----------------|-------------------------------|
|                       | No. of patients   | Per cent of patients improved | No. of patients | Per cent of patients improved |
| Marked                | 327               | 46                            | 74              | 36                            |
| Moderate              | 162               | 23                            | 40              | 19                            |
| Slight                | 65                | 9                             | 23              | 11                            |
| Unchanged             | 72                | 10                            | 24              | 12                            |
| Worse                 | 23                | 3                             | 6               | 3                             |
| Late deaths           | 56                | 8                             | 39              | 19                            |
| Totals                | 705               |                               | 206             |                               |

#### FACTORS INFLUENCING THE IMPROVEMENT OF PATIENTS FOLLOWING SURGERY

The factors that might have an effect on the postoperative course of patients are so numerous that it is impossible to analyze them for each year of follow-up. Therefore, the over-all improvement status is given on the basis of the patients' condition at the last follow-up.

Sixty-nine per cent of group-II and III patients and 55 per cent of the group-IV patients have improved (table 7). In analyzing the effect of certain factors on the improvement it is necessary to compare as homogeneous groups as possible. Therefore statistical analyses have been made on groups in which all the patients have been followed for 1 and also for 5 years, and the status at the end of the 1 and 5-year periods has been recorded. In table 8 the improvement at the end of 5 years is analyzed according to age, sex, and rhythm. It will be seen that male and female patients in group III improved to approximately the same degree. Patients in this group in normal rhythm were improved to a greater extent than those who were fibrillating, since the *p* value for this correlation is between 0.05 and 0.02. There is a tendency for patients over 40 to do somewhat less well than the younger patients (*p* between 0.02 and 0.01). There are more fibrillating patients in the group over 40; nevertheless both age and rhythm play significant roles as the adjusted rates show.

In group IV significant differences due to age, sex, or rhythm are not apparent, although the same tendencies are observed as in group III.

The figures for improvement by age, sex, and rhythm at the end of 1 year of follow-up show the same tendencies that were observed at 5 years, although differences become more striking at the 5-year period.

Of interest are the results in relation to the findings at the time of operation. These include the degree of mitral stenosis, the presence and amount of mitral insufficiency, and the adequacy of the valvuloplasty as estimated by the surgeon at the time of operation. There are a number of factors that affect the operative results, some of which are within the control of the surgeon, depending on his skill and experience, and others are inherent in the state of a valve as it is found at operation. These include the degree of calcification and its location, the rigidity of the leaflets, and the extent of fusion and shortening of the chordae tendineae. The quality of the valvuloplasty is of the greatest importance in long-term results.

With an increasing degree of mitral insufficiency, the results at the end of 5 years are progressively worse (table 8). The degree of insufficiency was that amount which was estimated to be present by the surgeon after completion of the valvuloplasty. In group III 78 per cent of patients with pure mitral stenosis were improved as compared to only 48 per cent of those showing 2-plus or greater regurgitation at the time of surgery. In group IV the improvement rate dropped from 69 to 36 per cent. These differences are all significant (*p* less than 0.01) except for the comparison of patients with no versus 1-plus insufficiency in group III, and between 1 plus versus 2 to 3-plus insufficiency in group IV.

If the same correlations are made at the end of 1 year instead of 5, then the difference in the degree of improvement between those with no insufficiency and those with increasing degrees of insufficiency is much less apparent

TABLE 8.—*Status at the End of One and of Five Years*

|                              | Groups II and III |                               |                 |                               |                 | Group IV        |                               |                 |                               |                |
|------------------------------|-------------------|-------------------------------|-----------------|-------------------------------|-----------------|-----------------|-------------------------------|-----------------|-------------------------------|----------------|
|                              | One year          |                               | Five years      |                               |                 | One year        |                               | Five years      |                               |                |
|                              | No. of patients   | Per cent of patients improved | No. of patients | Per cent of patients improved | Adjusted rates* | No. of patients | Per cent of patients improved | No. of patients | Per cent of patients improved | Adjusted rates |
| Sex                          |                   |                               |                 |                               |                 |                 |                               |                 |                               |                |
| Male                         | 151               | 83                            | 66              | 68                            |                 | 50              | 72                            | 26              | 50                            |                |
| Female                       | 554               | 85                            | 205             | 71                            |                 | 156             | 71                            | 64              | 57                            |                |
| Rhythm                       |                   |                               |                 |                               |                 |                 |                               |                 |                               |                |
| Normal sinus                 | 408               | 88                            | 158             | 78                            | 74              | 41              | 83                            | 20              | 65                            |                |
| Atrial fibrillation          | 297               | 80                            | 113             | 60                            | 63              | 165             | 69                            | 70              | 51                            |                |
| Age by decades               |                   |                               |                 |                               |                 |                 |                               |                 |                               |                |
| 10-19                        | 6                 | 100                           | 2               | 100                           |                 | 0               | —                             | —               | —                             |                |
| 20-29                        | 116               | 91                            | 52              | 81                            |                 | 5               | 80                            | 3               | 67                            |                |
| 30-39                        | 277               | 89                            | 115             | 76                            |                 | 42              | 74                            | 22              | 59                            |                |
| 40-49                        | 262               | 79                            | 93              | 63                            |                 | 94              | 76                            | 44              | 52                            |                |
| 50-59                        | 40                | 73                            | 9               | 11                            |                 | 56              | 63                            | 18              | 56                            |                |
| 60-69                        | 2                 | 100                           | —               | —                             |                 | 9               | 62                            | 3               | 33                            |                |
| Mitral insufficiency†        |                   |                               |                 |                               |                 |                 |                               |                 |                               |                |
| None                         | 401               | 88                            | 158             | 78                            | 77              | 84              | 77                            | 32              | 69                            | 61             |
| +                            | 174               | 86                            | 52              | 73                            | 72              | 56              | 80                            | 24              | 46                            | 45             |
| ++ & +++                     | 103               | 75                            | 40              | 48                            | 51              | 46              | 50                            | 22              | 36                            | 50             |
| Preoperative valve size†     |                   |                               |                 |                               |                 |                 |                               |                 |                               |                |
| 1.0 cm. <sup>2</sup> or less | 438               | 86                            | 198             | 76                            |                 | 144             | 84                            | 61              | 61                            |                |
| 1.1 cm. <sup>2</sup> or more | 240               | 84                            | 52              | 58                            |                 | 42              | 52                            | 17              | 24                            |                |

\*Adjusted rates calculated by indirect method.

†In a few patients clinical information regarding valve size or mitral insufficiency was lacking and these have been omitted from consideration.

It would appear, therefore, that the damaging effect of mitral insufficiency takes time to appear.

When patients are studied in respect to their improvement in relation to the preoperative valve size, it is apparent that the patients who had tight mitral stenosis, that is an estimated valve area of 1 cm.<sup>2</sup>, or less, did better at the end of 5 years than did patients whose valve area was larger. This is true in both group III and group IV. Again this difference was observed in patients when they were studied at the end of 1 year in group IV but was not apparent in group III.

The effects of increasing degrees of mitral insufficiency and of a larger preoperative valve size in militating against a successful

outcome were additive, as demonstrated by the adjusted rates.

The majority of these patients had only anterior fusion bridge fracture or valvulotomy incision. More recently a technic has been developed for the adequate fracture of the posterior fusion bridge as well. The effect of this "more adequate" (certainly more extensive) operation on sustained improvement, refluxion, or indeed deterioration from subsequent mitral insufficiency will be discussed in another communication. The technic of this operation is discussed elsewhere.<sup>2</sup>

The presence of associated valve disease had no statistically significant effect on the results at the end of 5 years in either group III or group IV.

#### IMPROVEMENT IN RELATION TO POSTOPERATIVE COMPLICATION

Following surgery many of the patients complained in varying degrees of symptoms not directly related to the status of their cardiac compensation. Some of these symptoms comprise a syndrome that has been reported under the term of "postoperative" or "post-commissurotomy syndrome," and is characterized chiefly by exacerbation of pain in the chest of varying types, with fever. There may be evidence of pericarditis, pleuritis, and pneumonitis in varying degrees. In our experience this situation has been benign and self-limited, lasting a week or 2 and has not appeared to be affected particularly by the type of therapy given, such as acetylsalicylic acid, penicillin, or adrenal steroids. The syndrome is considered by some to be an activation of rheumatic infection. In our experience, however, clear-cut evidence of rheumatic fever occurs in only a minority of patients. The syndrome tends to be recurrent and may appear for the first time several years after surgery and recurrences may occur over several years. The relation, therefore, to the surgical procedure is obscure. It has been pointed out by Ito, Engle, and Goldberg<sup>17</sup> that this syndrome also occurs in patients with nonrheumatic heart disease who have had intracardiac surgery involving opening of the pericardium and it is their opinion that this may represent recurring nonspecific pericarditis. We have no evidence bearing on this point, except that we have no patients with pericardial effusions in the postoperative period or later.

Since most of these patients have returned to their homes and have been observed by their local doctors, and only occasionally personally by us, the reported incidence of this syndrome cannot be accurate, and may include some cases of pneumonia or other respiratory infections as well as pulmonary infarctions.

The incidence of the postoperative syndrome occurring in these patients was 30.8 per cent (30.4 per cent for group III and 32.2 per cent for group IV). This is comparable

to that previously reported for the first 500 patients of this series followed for a shorter time,<sup>3</sup> as well as reports of others. It is of interest, however, that the over-all improvement of patients suffering from the postoperative syndrome is essentially the same as for the groups as a whole (68 per cent in group III and 51 per cent in group IV).

Many patients complain also of vague joint pains. Whether the incidence of such joint pains is any higher in this group of patients than it would be in any other carefully followed group of middle-aged people with chronic disease is uncertain. We have divided our patients into those who have suffered from arthralgias only, and those who had a clear-cut arthritis, sometimes of the rheumatoid type, but with no clear evidence of rheumatic fever. A history of arthralgia or of arthritis did not affect the results strikingly, but in both groups III and IV the patients in whom rheumatic fever was diagnosed did poorly. This will be discussed in a later section.

#### IMPROVEMENT IN RELATION TO THE PRESENCE OF ASCHOFF BODIES IN THE BIOPSY OF THE LEFT ATRIAL APPENDAGE

In a previous study<sup>20, 21</sup> the relationship of the presence of Aschoff bodies in biopsies of the left atrial appendages to the clinical findings was reported. The present study confirms the previous one. The biopsy reports utilized in the present study were routine reports received from the pathologic laboratories of the several hospitals concerned. No attempt was made to have the microscopic findings reviewed by a single pathologist as was the case in the earlier study. A total of 632 biopsy reports are available from this series of 1,000 cases. In the group-III patients 43 per cent were positive. In group IV the incidence of positive biopsies was 20 per cent. Table 9 shows that the incidence of positive biopsies is greatest in the younger age groups and falls progressively with increasing age but is still 21 per cent in the 50 to 59 decade group in group III and 18 per cent in group IV. The

TABLE 9.—Incidence of the Finding of Aschoff Bodies in 632 Atrial Biopsies

| Rhythm              | No. of patients | Per cent with positive biopsies |                   | Improved at last follow-up |                   |
|---------------------|-----------------|---------------------------------|-------------------|----------------------------|-------------------|
|                     |                 | Positive biopsies               | Negative biopsies | Positive biopsies          | Negative biopsies |
| Normal sinus        | 328             | 54                              | 74                | 72                         |                   |
| Atrial fibrillation | 304             | 18                              | 63                | 64                         |                   |

| Age by decades | Group III       |                                 |                                 |                                 | Group IV        |                                 |                                 |                                 |
|----------------|-----------------|---------------------------------|---------------------------------|---------------------------------|-----------------|---------------------------------|---------------------------------|---------------------------------|
|                | No. of patients | Per cent with positive biopsies | Improvement % positive biopsies | Improvement % negative biopsies | No. of patients | Per cent with positive biopsies | Improvement % positive biopsies | Improvement % negative biopsies |
| 10-19          | 5               | 60                              | 100                             | 50                              | —               | —                               | —                               | —                               |
| 20-29          | 79              | 63                              | 79                              | 79                              | 4               | 50                              | —                               | —                               |
| 30-39          | 200             | 46                              | 74                              | 75                              | 35              | 26                              | 75                              | 61                              |
| 40-49          | 181             | 35                              | 65                              | 68                              | 68              | 16                              | 60                              | 58                              |
| 50-59          | 24              | 21                              | 75                              | 63                              | 33              | 18                              | 80                              | 62                              |
| 60-69          | 1               | —                               | —                               | 100                             | 2               | —                               | —                               | 50                              |
| Total          | 490             | 43                              |                                 |                                 | 142             | 20                              |                                 |                                 |

positive biopsies are much more likely to be found in any age group in the patients with normal sinus rhythm than in patients with atrial fibrillation. Both of these findings confirm our previous report. When patients are compared by age groups, the percentage improvement of those with positive biopsies was the same as of those with negative biopsies.

When the incidence of positive biopsies is correlated with the occurrence of the various postoperative complications, no relation is evident. The percentage of positive biopsies in patients later developing the postoperative syndrome was nearly the same as for the group as a whole (40 per cent in group III, 15 per cent in group IV). Patients who subsequently developed definite rheumatic fever tended to have a slightly but not impressively higher incidence of positive biopsies (56 per cent).

#### FACTORS INVOLVED IN THE DETERIORATION OF PATIENTS WHO HAVE IMPROVED FOLLOWING MITRAL VALVULOPLASTY

Two hundred twenty-eight of the patients in this study have become worse after having been significantly improved, that is "markedly" or "moderately," for at least 1 year

after valvuloplasty. For the sake of this analysis, the definition of "deterioration" is that they have slipped by at least 1 class, according to the American Heart Association classification. Sixty-two of these patients slipped only from "markedly" to "moderately" improved, and hence would still be classed in the "improved" category. The remaining 166 deteriorated from either being originally "markedly" or "moderately" improved into the "unimproved" classification; that is, they are now either only "slightly" improved, their condition is unchanged as compared to the preoperative state, they are worse, or dead. Of these patients, 48 have died since operation, and 45 have been reoperated on for mitral valvular disease. These patients were not all personally observed by the authors at the time of their deterioration; evidence for their deterioration was obtained in some from their answers to annual questionnaires or from letters from their physicians.

There are a number of factors that may have been of importance in these 228 patients in producing the deterioration of these patients. Many of these occurred in combination. In 56 mitral insufficiency was present, either alone or in combination with other fac-

TABLE 10.—*Influence of Significant Mitral Insufficiency Found or Produced at Operation\**

| Status of patients                                      | Patients followed five years |                                    | All patients at latest follow-up |                                    |
|---|------------------------------|------------------------------------|----------------------------------|------------------------------------|
|   | No. of patients              | Per cent with mitral insufficiency | No. of patients                  | Per cent with mitral insufficiency |
| Patients who deteriorated after substantial improvement | 89                           | 30                                 | 222                              | 22                                 |
| Patients who maintained improvement                     | 196                          | 12                                 | 531                              | 12                                 |
| Patients who failed to improve                          | 43                           | 28                                 | 113                              | 35                                 |

\*Patients in whom there were no adequate records of the presence or absence of mitral insufficiency have been omitted from consideration.

tors, at the time of surgery. This mitral insufficiency was of moderate to marked extent, and was either present prior to fracture of the valve or was produced at the time of surgery. From this particular study, it is, of course, impossible to say to what extent mitral insufficiency may have developed or increased both in patients in whom it had been previously recognized and in those in whom it had not been suspected.

In table 10 there is shown a comparison of 3 groups of patients all of whom have been followed for 5 years and thus can be compared on a statistical basis. It will be seen that patients from the present group who deteriorated after substantial improvement as well as patients who failed to improve at all exhibited mitral insufficiency at the time of operation much more often than did patients who showed a maintained improvement ( $p$  less than 0.01). There is no significant difference between the patients who deteriorated and those who failed to improve.

The incidence of mitral insufficiency in these 3 groups has also been compared among all of the patients at the time of their latest follow-up and a trend similar to that shown in the 5-year group is apparent. The relatively lower

TABLE 11.—*Influence of an Unsatisfactory Correction of Mitral Stenosis\**

| Status of patients                                      | Patients followed five years |   | All patients at latest follow-up |   |
|---|------------------------------|---|----------------------------------|---|
|   | No. of patients              | Per cent with unsatisfactory correction | No. of patients                  | Per cent with unsatisfactory correction |
| Patients who deteriorated after substantial improvement | 93                           | 23                                      | 226                              | 17                                      |
| Patients who maintained improvement                     | 193                          | 9                                       | 513                              | 7                                       |
| Patients who failed to improve                          | 73                           | 15                                      | 123                              | 9                                       |

\*Patients in whom it was impossible to assess adequately the quality of the operative procedure have been omitted from consideration.

incidence of mitral insufficiency in the deteriorated group may possibly be due to the fact that mitral insufficiency takes time to produce its ravaging effect and the follow-up figures for the entire group include many patients followed less than 5 years.

At the time of operation, the surgeon was frequently unable to accomplish a fully satisfactory correction of the stenosis. This failure may have been due to conditions beyond his control, such as marked rigidity of the valve cusps, or widespread calcification or extreme shortening and fusion of the chordae tendineae. It is to be expected that with increasing experience a surgeon will become more skillful in effecting the maximum amount of correction while avoiding the production of insufficiency. There were 38 patients in the group of 228 who deteriorated, in whom an adequate correction of mitral stenosis was not effected at the time of operation, and 66 more in whom the correction was less than satisfactory. In table 11 a comparison is made of groups of patients followed for 5 years. Both the patients who deteriorated after substantial improvement and those who failed to improve at all were found to have an unsatisfactory correction of their stenosis in a much higher per-

centage than did those who have shown maintained improvement ( $p$  less than .01 for both). The percentage of unsatisfactory corrections was somewhat higher in those who deteriorated than in those who failed to improve at all, but the difference is not significant ( $p$  between .30 and .20). However it is suggestive that if the operations consisted chiefly of dilatation of the valve or temporary mobilization of the cusps, the patient may do well for a while.

This table also shows the results at the latest follow-up of all patients. Although the same trends are evident, the percentage figures are lower in all categories. This is due to the fact that the over-all follow-up also includes patients operated on in the last half of the series, who have been followed less than 5 years. The number of unsatisfactory operations performed in these recently operated patients was lower than in the earlier half of the series. Indeed the number of unsatisfactory operations in the earlier group is higher than it appears, for the surgeon must have at times failed to recognize an unsatisfactory valvuloplasty. With greater experience the surgeon becomes more exacting in his acceptance of "an adequate operation."

The role of rheumatic fever in causing deterioration in patients is even more striking. There were 38 patients in the group of 228 who had rheumatic fever sometime after surgery. Of those followed for 5 years, 19 per cent deteriorated after substantial improvement (table 12). In contrast, only 1.5 per cent of the patients showing maintained improvement and 9 per cent of those who failed to improve at all gave evidence of rheumatic fever. The differences between patients showing maintained improvement and the other 2 groups are significant ( $p$  less than 0.01) but the difference between deteriorated patients and those who failed to improve is not statistically significant ( $p$  0.10 to 0.05).

It is of course often difficult to make a clear-cut diagnosis of rheumatic fever in adults, and most of these patients were not personally seen by us. A diagnosis of rheumatic fever was only accepted in these pa-

TABLE 12.—*Influence of Rheumatic Fever Occurring Since Operation*

| Status of patients                                      | Patients followed five years |                               | All patients at latest follow-up |                               |
|---|------------------------------|-------------------------------|----------------------------------|-------------------------------|
|   | No. of patients              | Per cent with rheumatic fever | No. of patients                  | Per cent with rheumatic fever |
| Patients who deteriorated after substantial improvement | 95                           | 19                            | 228                              | 17                            |
| Patients who maintained improvement                     | 193                          | 1.5                           | 541                              | 2.2                           |
| Patients who failed to improve                          | 73                           | 9                             | 142                              | 14                            |

tients, however, if they had reasonably convincing evidence of it. Patients who suffered from one or more attacks of the postoperative syndrome, and those who complained merely of vague joint pains did not show any unusual tendency to deteriorate.

Associated aortic valve disease occurred in the group of 228 patients who did poorly after initial improvement in 10 per cent, which is about the same percentage as in the series as a whole (12 per cent). Other causes possibly involved in the deterioration were peripheral emboli resulting in death or disability in 8 patients and subacute bacterial endocarditis in 3. In 62, there were no obvious factors explaining their deterioration. In some of these cases, the deterioration was unquestionably related to noncardiac causes, such as emotional states sometimes associated with the menopause, or other neurotic factors.

What does this study of patients who deteriorated reveal? Firstly, it shows that recurrent rheumatic fever often leads to deterioration of the cardiac status in these patients just as it does in rheumatic cardiac patients in general.

Secondly, it shows that mitral insufficiency is an important cause of relapse and that in many cases this incompetence may be produced or increased by the operative procedure. In another study we observed that mitral in-

sufficiency which was thought to be minimal or even not to exist at all at a first operation had become a major factor at the time of re-operation. If this is true also in regard to the entire group of 228 who deteriorated, it is evident that mitral insufficiency may well play an even more important role than was indicated by the 22 per cent incidence found in this group at surgery. The implication of this finding in connection with patients who are being considered for re-operation for mitral stenosis is obvious, as well as for surgery in mitral stenosis in general. It is evident that significant mitral insufficiency may be produced by the surgeon at operation and this may constitute a warning against too extensive or poorly directed fracture of valves in an effort to produce a complete relief of the stenosis. This also means that patients who have deteriorated and are being considered for re-operation must be scrutinized very carefully for the presence of mitral insufficiency before a second operation for mitral stenosis, since the major problem may really be mitral incompetence rather than stenosis and the conventional operation will not suffice.

Thirdly, this study shows how important is the quality of the technical performance. Not only must the production of mitral insufficiency be avoided but inadequate surgery for the relief of stenosis must also be avoided since the patients with unsatisfactorily performed mitral valvuloplasties deteriorate in a much higher percentage than do those in whom a good job was done.

Fourthly, the factor of predominant myocardial failure may well exist in many of these patients.

Finally, it can be said that although re-stenosis of the mitral valve does occur, it is only one of several factors that are of importance in the deterioration of patients and significant re-stenosis requiring re-operation does not commonly occur if the original operation was adequately done. It is impossible, on the basis of these studies to give accurate figures as to the rate of occurrence of re-stenosis. There are too many variable factors.

#### DISCUSSION

A great many papers have appeared concerning the clinical results in patients operated on for mitral stenosis. Although for the most part the degree of improvement reported in these various articles is in general agreement with our findings, in the majority of reports the length of follow-up has been relatively short. However, the reports by Likoff and Uricchio<sup>22</sup> have dealt with patients followed for periods up to 8 years, and Glover et al.<sup>23</sup> reported a series of 50 patients followed 5 or more years. It has now been well demonstrated that patients with mitral stenosis can be operated upon with an acceptable operative mortality and that they are improved in the vast majority of instances. It is becoming apparent what factors are affecting this improvement, both immediately and over a long period of time. As we have pointed out previously, this is still a palliative operation although it is often life-saving and may be followed by extraordinary improvement that may persist for a long time. However, factors remain which lead in a substantial number of the patients to a gradual recurrence of difficulty in many of those who have improved, and militate against improvement in others. To some extent this has to do with the state of the valve itself. Even under the best of circumstances the valve remains in a scarred condition which may be conducive to recurrence of stenosis or to fixation of the leaflets, so that mitral incompetence results. The patient still remains a rheumatic subject, one in whom recurrence of rheumatic activity is ever possible. Studies such as ours have been of relatively negative value so far as elucidating the knotty problem of persistent or recurrent rheumatic activity in adults with chronic rheumatic heart disease. It is apparent that for the most part the criteria for rheumatic activity are not clear-cut and only in a minority of instances can a definite diagnosis be made. When undoubted rheumatic fever does take place after operation, however, the likelihood of cardiac deterioration is greatly enhanced.

The role of mitral insufficiency, either present prior to surgery or developing at the time of or subsequent to the operation, as an important factor leading to deterioration is becoming ever more apparent. Although true re-stenosis of the mitral valve may occur in some patients, this is not common in our experience nor in that of most observers. Bailey and his group<sup>24</sup> noted the increasing frequency of re-stenosis in the patients they are following over prolonged periods of time. It is apparent that symptoms of cardiac disability not infrequently recur in patients in whom the original operation was not fully satisfactory, either due to inexperience on the part of the surgeon or to other conditions. In any consideration of the problem of "re-stenosis," it is important to distinguish such recurrences after unsatisfactorily performed valvuloplasties from true re-fusion of the commissures after a completely satisfactory mobilization of the leaflets.

Myocardial failure is undoubtedly an important element in the poor results of some of the patients or in the deterioration of others. This has been pointed out by us and has been emphasized by Harvey and associates.<sup>25</sup> Whether myocardial failure follows from prolonged mechanical strain on the heart due to valvular defects or whether it is the result of the residual damaging effect of previous rheumatic myocarditis, or even of persistent rheumatic activity has not been satisfactorily elucidated, nor is it possible at times to make a definite distinction between myocardial failure and the mechanical factors resulting from valvular defects. Even with the aid of catheterization findings obtained by experienced investigators a definite diagnosis may not be made. Hemodynamic formulae have their limitations, not the least being the fact that the application of such formulae must be with data obtained only on isolated occasions and under the most abnormal circumstances, namely the situation of cardiac catheterization itself. We have observed on a number of occasions patients who, from catheterization findings, have what one would

call physiologic left ventricular failure although the patients had no symptoms or signs of clinical heart failure. Conversely, it is often possible for a patient to have manifestations of congestion without exhibiting hemodynamic manifestations of what one calls heart failure, namely an elevated left or right ventricular diastolic pressure.

It has been suggested<sup>25, 26</sup> that hemodynamic studies made before and after the administration of a parenteral digitalis or strophanthin preparation may help to distinguish the myocardial failure from the mechanical effects of the mitral block. Such tests are difficult to carry out and only valid in the hands of the most experienced investigators and hence could never have wide applications, even for such limited value as they may have. Most important of all, the quantitative evaluation of the relative degrees of stenosis versus regurgitation at a valve has as yet been accomplished only very imperfectly by catheterization or any other technics. A careful clinical evaluation is still as reliable as any of the special laboratory technics.

#### SUMMARY

A report has been made of the clinical results in 1,000 consecutive cases with a preoperative diagnosis of mitral stenosis that underwent valvuloplasty between 1949 and 1956. All but 2 of the 913 survivors of the operation have been followed at least 1 year and most of them up to the latest anniversary of their operation from 2 to 8 years ago.

When the preoperative clinical diagnosis was pure mitral stenosis, the surgeon confirmed the diagnosis at operation in about 90 per cent of cases, but when mitral stenosis and insufficiency was diagnosed preoperatively, operation revealed significant insufficiency in only about one half of the case.

The incidence of operative embolization in the second 500 of this series has been 2.1 per cent in group III and 8.0 per cent in group IV. In only 25 have peripheral emboli occurred since operation.

Including operative mortality, 83 per cent of group-III patients and 57 per cent of group-IV patients have survived 7 years. These figures are much higher than reported survival rates of medically treated patients. The effects of sex, rhythm, and age on survival have been discussed.

The over-all percentage of patients significantly improved by operation has been 69 per cent in group III and 55 per cent in group IV. The percentage improved has tended to drop somewhat with succeeding years of follow-up.

In group III, fibrillating patients and those over 40 years of age did less well than those in normal rhythm or under 40; there was, however, no difference due to sex. In group IV significant differences due to rhythm, age, or sex were not apparent.

With increasing degrees of mitral insufficiency the results were progressively poorer and the differences were more striking at the end of 5 years than at the end of 1 year. Patients with preoperative tight mitral stenosis (1.0 cm.<sup>2</sup> or less) did better than those whose stenosis was less severe. The presence of associated valve disease (usually aortic) of mild degree did not affect the ultimate outcome.

The "postoperative" or "postcommisurotomy" syndrome occurred in an estimated 30.8 per cent of patients, but its presence did not have any bearing on the results.

Aschöff bodies were described in the biopsies of atrial appendages in 43 per cent of group-III patients and in 20 per cent of group-IV patients. They were present in a higher percentage of patients in normal rhythm than those in fibrillation, and the incidence decreased progressively with age. The presence of a positive biopsy had no relation to the ultimate results or to the occurrence of the postoperative syndrome.

A group of 228 patients who deteriorated after substantial improvement persisting at least 1 year were analyzed. Factors that were found in a significantly higher percentage than in patients who maintained their improvement were mitral insufficiency, an unsatisfactorily performed valvuloplasty, and clear-cut rheumatic fever occurring since operation.

#### SUMMARY IN INTERLINGUA

Es reportate le resultatos clinic in 1.000 casos consecutive in que le diagnose preoperatori de stenosis mitral esseva sequite per valvuloplastia, effectuate inter 1946 e 1956. Con 2 exceptiones, omne le 913 superviventes del operation esseva tenite sub observation durante al minus un anno. In le majoritate del casos, le observation esseva extendite usque al plus recente anniversario del operation effectuate inter 2 e 8 annos retro.

Quando le diagnose clinic preoperatori esseva pur stenosis mitral, le chirurgo confirmava le diagnose al operation in circa 90 pro cento del casos, sed inter le casos in que stenosis e insufficiencia mitral esseva diagnosticate ante le operation, le incidentia de insufficiencia significative constatate per le chirurgo esseva solmente circa 50 pro cento.

Le incidentia de embolisation operatori inter le secunde 500 casos del serie esseva 2,1 pro cento in gruppo III e 8,0 pro cento in gruppo IV. Embolos peripherie ha occurrite deposit le operation in solmente 25 casos.

Prendente in consideration le mortalitate operatori, 83 pro cento de patientes de gruppo III e 57 pro cento de patientes de gruppo IV ha supervivite 7 annos. Iste cifras es multo plus alte que illos reportate pro le superviventia de patientes tractate per mesuras medical. Le effectos de sexo, rhythmo, e etate super le prognose es discutite.

Le procentage total del patientes significativamente meliorate per le operation esseva 69 pro cento in gruppo III e 55 pro cento in gruppo IV. Iste procentages monstrava un tendentia descendente in le curso del annos postoperatori.

In gruppo III, patientes con fibrillation e patientes de plus que 40 annos de etate habeva un prognose minus favorable que patientes con rhythmo normal e patientes de minus que 40 annos de etate. Tamen, nulle differentia esseva constatate secundo le sexo. In gruppo IV, nulle significative differentias esseva notate secundo rhythmo o etate o sexo.

Parallel al augmento del grado de insufficiencia mitral, le resultatos se pejorava progressivamente. Le differentias esseva plus frap

ante al fin de 5 annos que al fin de 1 anno. Patientes con tense stenosis mitral ante le operation (1 cm<sup>2</sup> o minus) reageva melio que patientes in qui le stenosis esseva minus sever. Le associate presentia de morbo valvular (usualmente aortic), si illo esseva de leve grados, non affieva le resultado final.

Le syndrome "postoperatori" o "postcommissurotomic" occorreva estimateamente in 30,8 pro cento del patientes, sed su presentia absentia no influentiava le resultado final.

Corpores de Aschoff esseva describe in le biopsias de appendages atrial in 43 pro cento del patientes de gruppo III e in 20 pro cento del patientes de gruppo IV. Illos esseva presente in plus alte porcentages in patientes con rhythmo normal que in patientes con fibrillation. Lor incidentia descendea progressiveamente con le avantiamento del etate. Le presentia de un biopsia positive habeva nulle relation con le resultado final o con le occurrentia o non-occurentia del syndrome postoperatori.

Esseva analysate le casos de un gruppo de 228 patientes in qui marcate grados de deterioration se declarava post un melioration substantial de un duration de al minus 1 anno. Factores que se trovava in iste casos in porcentages significativeamente plus alte que in casos in que le melioration se manteneva include insufficiencia mitral, un valvuloplastia non effectuate satisfactorimente, e le occurrentia de clar episodios de febre rheumatic depost le operation.

#### ACKNOWLEDGMENT

We are greatly indebted to Dr. Mindel Sheps of the Department of Preventive Medicine, Harvard Medical School, for her valuable advice and assistance in the statistical evaluation of the results. The collection of follow-up information and compilation of statistics were largely performed by Mrs. Georgiana, Mr. Arthur Spiro, and Mrs. Eleanor Angelokas.

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## Medical Eponyms

By ROBERT W. BUCK, M.D.

**Babinski's Phenomenon.** Joseph Francois Felix Babinski (1857-1932) described this sign in the *Comptes rendus hebdomadaires des Séances et Mémoires de la Société de Biologie* **48**: 207-208 (Feb. 22) 1896. The title of the article from which the following quotation is taken is "A Plantar Cutaneous Reflex in Certain Organic Affections of the Central Nervous System" (*Sur le Réflexe Cutané Plantaire dans Certaines Affections Organiques du Système Nerveux Central*):

"I have observed in a certain number of cases of hemiplegia or monoplegia involving the leg which were associated with an organic affection of the central nervous system, a disturbance in the plantar reflex of which I here present a short description: On the healthy side, pricking of the sole of the foot causes a flexion of the thigh on the pelvis, the leg on the thigh, the foot on the leg, and the great toe on the metatarsus. This occurs similarly in normal patients. On the paralyzed side, a similar stimulus also gives rise to a flexion of the thigh on the pelvis, the leg on the thigh, the foot on the leg, but the great toe, instead of being flexed, is extended on the metatarsus."

# Evaluation of Operability in Patients with Pulmonary Hypertension by Catheterization and Occlusion of Patent Ductus Arteriosus

By A. ACTIS-DATO, M.D., AND A. TARQUINI, M.D.

The authors describe a technic of temporary occlusion of the patent ductus arteriosus during right heart catheterization by a balloon filled with contrast medium connected to the tip of the catheter. This procedure is a valuable aid in the selection of patients with patent ductus arteriosus and severe pulmonary hypertension for operation.

AS REPORTED by various authors,<sup>1-5</sup> surgical closure of a patent ductus arteriosus with pulmonary hypertension presents a considerable operative risk. In fact, in these cases the patent ductus may constitute a safety valve for the hypertensive lesser circulation and its surgical closure may therefore suddenly increase the pulmonary hypertension with resultant acute right ventricular strain.<sup>3</sup>

The advisability of operation in these cases always presents a difficult problem. We have studied whether better surgical evaluation could be made by studying right-sided hemodynamic changes following temporary occlusion of the ductus (by an inflatable balloon) during cardiac catheterization.

There is almost general agreement on the advisability of surgical treatment when the pulmonary pressure is moderate or slightly elevated (40 to 80 mm. Hg) though the operative risk is increased. The problem appears to be far less simple when the pulmonary hypertension is notably increased (up to 90 mm. Hg or higher).

The pulmonary hypertension may be due to (1) increased blood flow in the pulmonary bed, (2) disease of the pulmonary vessels secondary to the increased blood flow, or (3) congenital lesion or irreversible alteration of the pulmonary vessels.<sup>1, 2, 4, 6-13</sup> In the first instance surgical occlusion of the ductus is indicated because one thereby reduces the

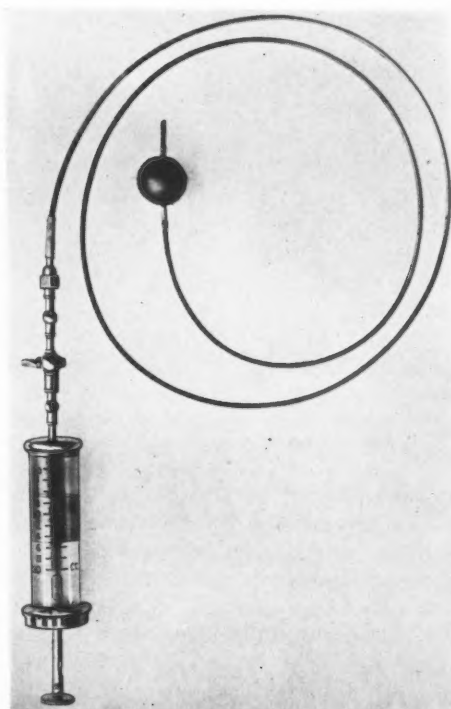


FIG. 1. Catheter bearing on its tip a balloon. The syringe connected to the catheter is used to fill the balloon with contrast medium.

blood flow in the pulmonary bed. In the second case surgical occlusion may halt or even lead to reversal of the pulmonary artery pathology. One should not operate when the pulmonary hypertension is due to congenital lesions of the pulmonary vessels or when the pulmonary pressure is the same or higher than the systemic blood pressure.

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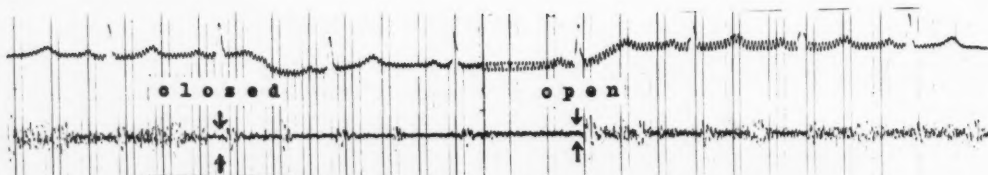


FIG. 2. Phonocardiographic recording in a case without pulmonary hypertension. The typical continuous murmur disappears after occlusion of the ductus arteriosus.

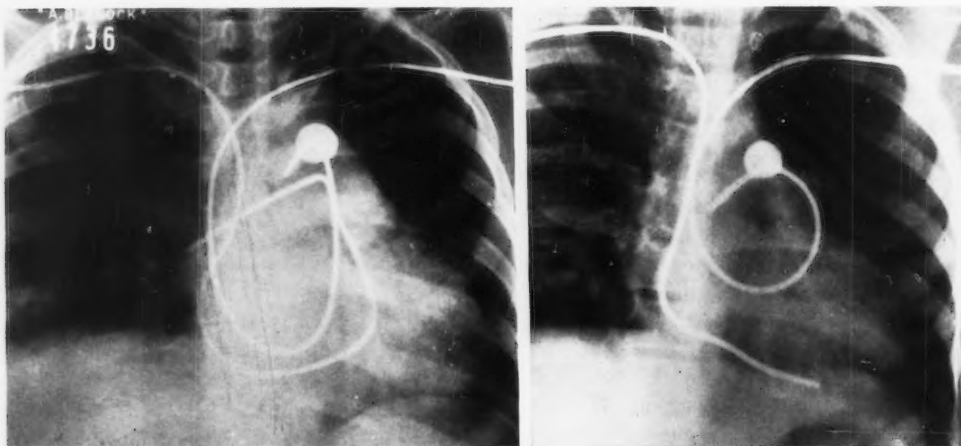


FIG. 3. The ductus arteriosus is occluded by the catheter balloon technique. By means of a second catheter introduced in the pulmonary artery (*left*) or in the right ventricle (*right*) measurement of pressures and sampling of blood are possible during the occlusion of the ductus.

Preoperative differentiation of these 3 categories is difficult; therefore many surgeons<sup>3-14</sup> base their decision on the changes in pulmonary artery pressure when the ductus is temporarily occluded during thoracotomy. If the pressure in the pulmonary artery falls or remains unchanged, the ductus is closed permanently; should the pressure increase, the ductus is left open. Other authors<sup>15</sup> have performed preliminary biopsy of lung tissue in patients with patent ductus arteriosus and pulmonary hypertension to determine whether organic arteriolar lesions are present. Others have suggested pharmacodynamic tests or variation of the oxygen tension in the inspired air during cardiac catheterization to evaluate the functional component of pulmonary hypertension and the extent of its reversibility.<sup>1-16</sup>

All methods are often unsatisfactory and there is always a serious risk in exploratory

operations in these patients; we have had one death.

Moreover, the valuation of the degree of pulmonary arteriopathy on a small fragment of lung tissue may be inadequate because of irregular distribution and the difficulty in appraising its functional significance. Since September 1956 we have developed a new technique for preoperative investigation of patients with patent ductus arteriosus and pulmonary hypertension.<sup>17, 18</sup>

By this technique it is possible during right heart catheterization to occlude the ductus arteriosus temporarily and to observe the hemodynamic changes in the right side of the heart and in the systemic circulation.

#### METHOD

A catheter with a small balloon on its tip (fig. 1) is advanced in the usual way from the right ventricle and pulmonary artery through the

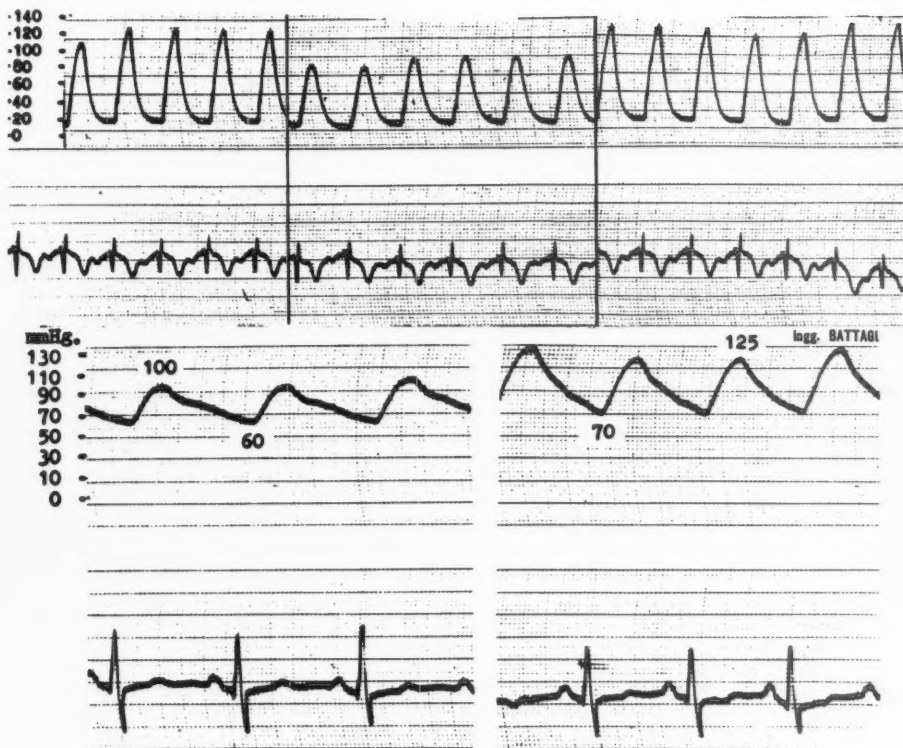


FIG. 4 Top. Case 2. Pressures (mm. Hg) in right ventricle; *left*, patent; *middle*, closed; *right*, opened. Note decrease of systolic pressure after closure of the ductus arteriosus and return to the previous values after removal of the balloon. The patient was operated on with good results.

FIG. 5 Bottom. Case 3. Pressures registered in the pulmonary artery. *Left*, before; *right*, after. Note increase in pressure after temporary occlusion of the ductus by means of the catheter balloon technic. Operation was not performed.

ductus to the aorta. The balloon is then expanded by filling it with a contrast medium. By exerting continuous gentle traction on the catheter the ductus is occluded at its aortic end.

When the ductus is completely closed the typical murmur disappears (fig. 2).

Since pulling the catheter produced some undesirable complications, such as tricuspid insufficiency (by traction on the tricuspid valve) and ventricular premature contractions, a modification has been devised by which traction of the catheter is no longer necessary. At the present time we use a double-lumen catheter bearing 2 balloons on its tip, 3 to 4 mm. apart; on inflation of the 2 balloons the ductus is closed at both ends.

Another catheter is introduced in the pulmonary artery or right ventricle (fig. 3) to allow

determination of pressure changes before, during, and after occlusion of the ductus. Changes of pulmonary blood flow are also calculated from blood samples from the pulmonary artery and the brachial artery. Observations may be made for 5 to 15 minutes.

During temporary closure of the ductus pulmonary artery and right ventricular pressures may drop, may rise, or may remain unchanged. With a drop, surgical occlusion of the ductus is definitely indicated, and with a rise it is definitely contraindicated. When there is no change we believe the operation is indicated, but pressures should be measured during effort, such as working at an ergometer while the ductus is kept closed with the balloon. If the pulmonary pressure rises under effort, we believe operation is not advisable.

TABLE 1.—Data from Six Patients with Patent Ductus Arteriosus and Pulmonary Hypertension

| Case no.                              | 1. N.T. | 2. M.Z.                       | 3. M.M.  | 4. M.Mi. | 5. M.S.<br>Before<br>surgery | 5. M.S.<br>1 yr. after<br>operation | 6. M.F.<br>Before<br>surgery  | 6. M.F.<br>2 yr. after<br>operation |
|---------------------------------------|---------|-------------------------------|--|----------|------------------------------|-------------------------------------|-------------------------------|-------------------------------------|
| Sex                                   | F       | F                             | F  | F        | M                            | M                                   | F                             | F                                   |
| Age                                   | 9       | 12                            | 15   | 34       | 8                            | 9                                   | 24                            | 25                                  |
| Cyanosis                              | +++     | +++                           | +++  | ++       | ++                           | —                                   | +++                           | ++                                  |
| Clubbing                              |         |                               |  |          |                              |                                     |                               |                                     |
| Upper limb                            | —       | —                             | —  | +        | —                            | —                                   | ++                            | ++                                  |
| Lower limb                            | +++     | ++                            | +++  | ++       | —                            | —                                   | +++                           | ++                                  |
| Dyspnea                               | +++     | +++                           | +++  | +++      | +                            | —                                   | +++                           | +                                   |
| Palpitation                           | +++     | +++                           | +++  | +++      | +                            | —                                   | ++++                          | +                                   |
| Hemoptysis                            | —       | —                             | —  | —        | —                            | —                                   | —                             | —                                   |
| Epistaxis                             | —       | —                             | —  | —        | —                            | —                                   | +++                           | —                                   |
| Broncho-<br>pneum.                    | +++     | +++                           | +++  | +++      | +++                          | —                                   | +++                           | —                                   |
| Physic-fitness<br>grading<br>(A.H.A.) | 2       | 1                             | 2  | 3        | 1                            | 0                                   | 2                             | 1                                   |
| Pressures Pulmonary A                 |         |                               |  |          |                              |                                     |                               |                                     |
| with<br>ductus<br>patent              | 110/75  | Right<br>ventr.<br>130/10     | 100/60   | 130/60   | 115/85                       | 60/35                               | 130/65                        | 50/20                               |
| with<br>ductus<br>closed              | 120/90  | Right<br>ventr.<br>90/10      | 125/70   | 150/65   | 90/80                        | —                                   | 130/65                        | —                                   |
| Aorta                                 | 110/70  | 140/90                        | 95/60  | 110/70   | 120/90                       | —                                   | 120/70                        | —                                   |
| O <sub>2</sub> blood saturation (%)   |         |                               |  |          |                              |                                     |                               |                                     |
| with ductus<br>patent                 |         |                               |  |          |                              |                                     |                               |                                     |
| R.B.A.                                | 83      | 95                            | 91   | 92       | 94                           | 95                                  | 96                            | —                                   |
| L.B.A.                                | 82      | 95                            | 89   | 89       | 92                           | 95                                  | 94                            | —                                   |
| Ductus<br>open F.A.                   | 79      | 90                            | 79   | 71       | 93                           | —                                   | 84                            | —                                   |
| Ductus<br>closed F.A.                 | 82      | 95                            | 90   | 92       | 94                           | 95                                  | 95                            | 95                                  |
| Murmur                                |         |                               |  |          |                              |                                     |                               |                                     |
| Systolic                              | +++     | +                             | not  | not      | ++                           | —                                   | +++                           | +                                   |
| Diastolic                             | —       | —                             | not  | not      | —                            | —                                   | —                             | —                                   |
| Continuous                            | —       | —                             | not  | not      | not                          | —                                   | —                             | —                                   |
| Operation                             | None    | Operated<br>(Large<br>ductus) | Explora-<br>tory<br>operation<br>(Large<br>ductus) | None     | Oper-<br>ated                | —                                   | Operated<br>(Large<br>ductus) | —                                   |
| Results                               | —       | Satis-<br>factory             | Death  | —        | Good                         | —                                   | Good                          | —                                   |

R.B.A., Right brachial artery; L.B.A., Left brachial artery; F.A., Femoral artery.

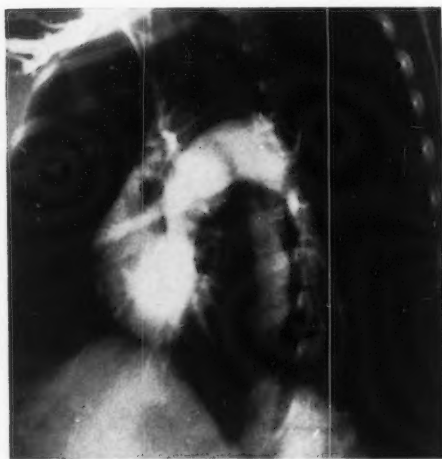


FIG. 6. Case 3. Angiocardiography. Visualization of the right heart and the pulmonary artery. Note the simultaneous visualization of the descending aorta by shunting of contrast medium through the patent ductus arteriosus (reversed shunt).

#### RESULTS

We have studied 6 patients (table 1). In 3 pulmonary artery and right ventricular pressures dropped after occlusion of the ductus (fig. 4), and surgical closure of the ductus was followed by marked clinical improvement, which was confirmed in cases 5 and 6 by data of a second catheterization performed 1 and 2 years later. Two other patients in whom the pulmonary pressure increased after occlusion of the ductus were not operated on. The sixth patient (case 3) showed a rise of the pulmonary pressure following the occlusion of the ductus (fig. 5) and reversal of the shunt (fig. 6).

Since the patients insisted on operation, an exploratory operation was done, a sudden significant rise of the pulmonary pressure with tachycardia occurred after temporary occlusion, and the ductus was left open. Eleven days later this patient died in cardiac failure.

#### SUMMARY

The technic of temporary occlusion of the patent ductus arteriosus during right heart catheterization provides useful data for eval-

uation of patients with ductus arteriosus complicated by severe pulmonary hypertension with or without reversed shunt.

A fall in pulmonary arterial pressure following closure of the ductus with the balloon is an indication for surgical occlusion. A rise of blood pressure in the pulmonary artery following the closure of the ductus is a contraindication. When the pressure remains unchanged the patient is subjected to moderate effort; then a rise of pressure is a contraindication for the operation.

No difficulties or complications have been encountered.

#### SUMMARIO IN INTERLINGUA

Le technica del oclusion temporari de patente ductos arteriose per catheterismo dextero-cardiac provide datos utile in evaluar le stato de pacientes con patente ducto arteriose, complicate per sever hypertension pulmonar con o sin shuntings revertite.

Un reduction del tension pulmono-arterial post clausura del ducto per medio del ballon de catheter es un indication pro effectuar oclusion chirurgic. Un augmento del tension de sanguine pulmono-arterial es un contraindication.

Nulle difficultates o complicationes esseva incontrate.

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I began to bethink my self if it might not have a circular motion, which afterwards I found true, and that the blood was thrust forth and driven out of the heart by the arteries into the habite of the body and all parts of it, by the beating of the left ventricle of the heart, as it is driven into the Lungs through the vena arteriosa by the beating of the right, and that it does return through the little veins into the vena cava, and to the right ear of the heart, as likewise out of the lungs through the aforesaid arteria venosa to the left ventricle, as we said before.

Which motion we may call circular, after the same manner that Aristotle says that the rain and the air do imitate the motion of the superiour bodies.—WILLIAM HARVEY. *De Motu Cordis*, 1628.

# Relationship between Diuretic and Antihypertensive Effects of Chlorothiazide and Mercurial Diuretics

By WILLIAM HOLLANDER, M.D., ARAM V. CHOBANIAN, M.D., AND  
ROBERT W. WILKINS, M.D.

Both chlorothiazide and parenteral mercurial diuretics have an antihypertensive as well as a natriuretic action. Previous observations have suggested that the antihypertensive effect is not due solely to sodium depletion. This paper expands these observations on a larger group of normotensive and hypertensive subjects and presents new studies on the effects of fluorohydrocortisone and SC-8109 (a "steroidal antagonist"), upon the sodium excretion and blood pressure of hypertensive patients during treatment with one of the diuretics.

**O**RAL chlorothiazide has been shown by a number of workers to be effective as an antihypertensive as well as a diuretic agent.<sup>1-15</sup> Parenteral mercurial diuretics likewise have been found to exert a hypotensive action in hypertensive subjects with or without complicating heart failure.<sup>12, 13, 16</sup> Although the mode of action of these diuretic agents on the blood pressure has not been clearly determined, clinical and laboratory observations have suggested that the antihypertensive effects of chlorothiazide may not be due solely to sodium depletion but might result in part from some other action to the drug.<sup>9, 12, 13</sup>

The current study presents further observations on the relationship between the saluretic and hypotensive actions of chlorothiazide and of the mercurial diuretics.

## MATERIAL AND METHODS

Twenty ambulatory normal subjects,\* most of whom were medical students, were given oral chlorothiazide after a 1- to 2-week control period. They were maintained on the drug during an unrestricted dietary salt intake for 30 days at a dose of 250 mg. of chlorothiazide 3 times a day. Observations of blood pressure and weight were recorded daily.

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Supported in part by a grant from the National Heart Institute, U. S. Public Health Service and by Merck Sharp and Dohme and Company, Inc.

\*Fifteen of these subjects were previously reported.<sup>12, 13</sup>

In addition, similar observations of blood pressure responses to the parenteral administration of chlorothiazide or of a mercurial diuretic were made in 15 normal and in 15 hypertensive ambulatory subjects without complicating heart failure. The hypertension was of the "essential" type except in 3 subjects who had an antecedent history suggesting either pyelonephritis or renal vascular disease. After preliminary control observations of blood pressure were obtained every 15 to 20 minutes for 3 hours, chlorothiazide was given intravenously in a dose of 1.0 Gm. over a period of 60 to 90 seconds. In the same or other individuals mercaptomerin or meralluride was injected subcutaneously or intravenously in a 2-ml. dose. After the administration of the diuretic, blood pressure was determined at intervals of 15 to 30 minutes for the first 8 hours and thereafter 8 times daily for the next 4 to 5 days. Weight was recorded before and after the administration of the diuretic. Urine was collected for the 24 hours following the injection.

Similar renal excretory and blood pressure studies were made of the effects of chlorothiazide or of a mercurial diuretic in 8 hypertensive subjects during known dietary salt intakes and following the administration of 9- $\alpha$ -fluorohydrocortisone or of SC-8109,\* a steroidal lactone. Seven of these subjects had essential hypertension and 1, C.L., had hypertension associated with occlusion of the right renal artery. Two subjects, C.L. and E.M., had been subjected to splanchnicectomy (Smithwick) more than 1 year prior to the present study without having a marked reduction in blood pressure. All subjects had a sustained elevation of the blood pressure with grade 2 retinopathy but without complicating congestive heart failure or nitrogen retention. For at least 6 weeks prior to the study all antihypertensive drugs had been withdrawn but the dietary intake of salt was unrestricted.

\*Kindly supplied by G. D. Searle and Company.

TABLE 1.—Summary of Data

|   | Systolic<br>blood<br>pressure<br>(mm. Hg) | Diastolic<br>blood<br>pressure<br>(mm. Hg) | Weight<br>(Kg.) |
|---|---|--|-----------------|
| Oral chlorothiazide in twenty normal subjects                   |   |  |                 |
| Control   | 117±5                                     | 74±5                                       | 75.1±10.3       |
| Chlorothiazide  | 117±5                                     | 74±6                                       | 74.7±10.2       |
| Mean difference   | 0±2                                       | 0±2  | -0.4± 1.1       |
| p   | 0.6                                       | 0.7  | 0.2             |
| Intravenous chlorothiazide in ten normal subjects               |   |  |                 |
| Control   | 115±6                                     | 72±8                                       | 77.2±12.6       |
| Chlorothiazide  | 114±7                                     | 74±8                                       | 76.0±12.6       |
| Mean difference   | -1±5                                      | +2±4                                       | -1.2± 0.5       |
| p   | 0.4                                       | 0.2  | <0.1            |
| Intravenous chlorothiazide in twelve hypertensive subjects      |   |  |                 |
| Control   | 202±16                                    | 114±11                                     | 63.2±15.9       |
| Chlorothiazide  | 172±26                                    | 102±16                                     | 62.4±15.7       |
| Mean difference   | -30±23                                    | -12±16                                     | -0.8± 0.3       |
| p   | <.01                                      | 0.03                                       | <.01            |
| Parenteral mercurial diuretics in fifteen normal subjects       |   |  |                 |
| Control   | 118±9                                     | 75±9                                       | 76.4±11.7       |
| Mercurials  | 119±11                                    | 75±9                                       | 75.4±11.5       |
| Mean difference   | +1±6                                      | 0±7  | -1± 0.9         |
| p   | 0.7                                       | 0.9  | <.01            |
| Parenteral mercurial diuretics in fifteen hypertensive subjects |   |  |                 |
| Control   | 196±22                                    | 117±12                                     | 67.1±14.4       |
| Mercurials  | 175±32                                    | 105±19                                     | 66.2±14.0       |
| Mean difference   | -21±20                                    | -12±12                                     | -0.9± 0.7       |
| p   | <.01                                      | <.01                                       | <.01            |

One potassium balance study and 9 sodium balance studies were carried out over a period of 16 to 32 days. In order to avoid the possible effect of hospitalization and bed rest on the blood pressure, all of these subjects with the exception of C.L., H.L., and E.M. were studied while ambulatory. Daily meals, which contained a total of 9 mEq. of sodium, were prepared by the dietary department and given in the hospital. Sodium intake was adjusted by adding or withdrawing weighed amounts of sodium chloride from the basic diet. The daily potassium intake in patient H.L. was controlled at 75 mEq. by supplementing the diet each day with weighed amounts of potassium chloride. Total urine output was collected daily and analyzed for creatinine, sodium, and potassium. Serum was also analyzed for these constituents. Weight was recorded before breakfast each day and the blood pressure was measured by the auscultatory method at least 6 times throughout the day.

Serum and urinary sodium and potassium were determined by the internal standard flame photometer (lithium standard). Creatinine in the serum and urine was determined by the method of Hare.<sup>17</sup>

## RESULTS

The effects of chlorothiazide and of parenteral mercurial diuretics on the blood pressure in normotensive and hypertensive subjects are presented statistically in table 1. The effects of these agents on blood pressure and salt excretion in hypertensive individuals are summarized in tables 2 to 5 and figures 1 to 5.

### Blood Pressure Effects of Chlorothiazide

In contrast to the hypotensive action of oral chlorothiazide in arterial hypertension,<sup>9</sup> 20 normal subjects had no significant reduction in blood pressure after 30 days on oral chlorothiazide in doses of 250 mg. 3 times daily. During the first week on the drug a weight loss of 0.5 to 2 Kg. usually occurred but without a change in blood pressure. However, by the end of the drug period there was no significant reduction in weight when compared with pre-drug values. The normotensive group likewise had no significant change in blood pressure following the intravenous injection of 1 Gm. of chlorothiazide although they did have a significant diuresis and a temporary reduction in weight.

In contrast with the normal subjects, 7 of 12 hypertensive subjects had an appreciable reduction in blood pressure varying from 20/15 to 60/30 mm. Hg following the intravenous injection of 1 Gm. of chlorothiazide. The hypotensive effect usually began within 12 to 18 hours and lasted for 24 to 48 hours. In addition to a reduction in blood pressure, chlorothiazide produced a significant diuresis and a temporary reduction in weight comparable to its effects in the normotensive controls.

### Blood Pressure Effects of Parenteral Mercurial Diuretics

Parenteral mercaptopurin or meralluride had a significant hypotensive action in 8 of 15 subjects with arterial hypertension but in none of the 15 normal individuals. The reduction in blood pressure in the hypertensive group ranged from 15/10 to 60/40 mm. Hg.

The hypertensive subjects who had a reduction in blood pressure following the administration of the mercurial diuretics also had

TABLE 2.—*Intravenous Chlorothiazide in Hypertensive Subject, M.L., Age 42*

| Balance day | Drugs                                       | Average blood pressure (mm. Hg) | Weight (Kg.) | Sodium intake (mEq./day) | Urinary sodium excretion (mEq./day) | Daily sodium balance (mEq./day) | Cumulative sodium balance (mEq.) |
|-------------|---|---------------------------------|--------------|--------------------------|-------------------------------------|---------------------------------|----------------------------------|
| 1           | Oral placebo                                | 192/114                         | 50.9         | 9                        | 59                                  | -50                             | -50                              |
| 2           | Oral placebo                                | 196/116                         | 51.1         | 9                        | 48                                  | -39                             | -89                              |
| 3           | Oral placebo                                | 199/118                         | 50.1         | 9                        | 25                                  | -16                             | -105                             |
| 4           | Oral placebo                                | 192/113                         | 49.9         | 9                        | 47                                  | -38                             | -143                             |
| 5           | Oral placebo                                | 198/115                         | 49.5         | 9                        | 4                                   | +5                              | -138                             |
| 6           | Chlorothiazide—1 Gm. I.V.<br>+ Oral placebo | 192/111                         | 49.9         | 9                        | 67                                  | -58                             | -196                             |
| 7           | Oral placebo                                | 160/92                          | 48.9         | 9                        | 1                                   | +8                              | -188                             |
| 8           | Oral placebo                                | 163/92                          | 49.2         | 9                        | 1                                   | +8                              | -180                             |
| 9           | Oral placebo                                | 165/94                          | 49.4         | 9                        | 1                                   | +8                              | -172                             |
| 10          | Oral placebo                                | 162/91                          | 49.4         | 9                        | 1                                   | +8                              | -164                             |
| 11          | Oral placebo                                | 160/90                          | 49.5         | 9                        | 2                                   | +7                              | -157                             |
| 12          | Oral placebo                                | 164/93                          | 49.4         | 9                        | 1                                   | +8                              | -149                             |
| 13          | Oral placebo                                | 182/108                         | 49.9         | 145                      | 10                                  | +135                            | -14                              |
| 14          | Oral placebo                                | 194/114                         | 50.8         | 145                      | 76                                  | +69                             | +55                              |
| 15          | Oral placebo                                | 195/113                         | 50.6         | 145                      | 166                                 | -21                             | +34                              |
| 16          | Oral placebo                                | 197/115                         | 50.6         | 145                      | 141                                 | +4                              | +38                              |

had a similar blood pressure response to intravenous chlorothiazide. The onset of the antihypertensive effect of either meralluride or mercaptopimerin occurred within 10 to 20 hours and lasted for 24 to 54 hours. Although the normal individuals had no significant change in blood pressure following mercurial injection, they did have an increased urinary output and a reduction in weight comparable to those observed in hypertensive individuals.

**Balance Study 1.** The effects of oral chlorothiazide on the blood pressure and sodium and potassium excretion in subject, H.L., with essential hypertension are shown in figure 1.

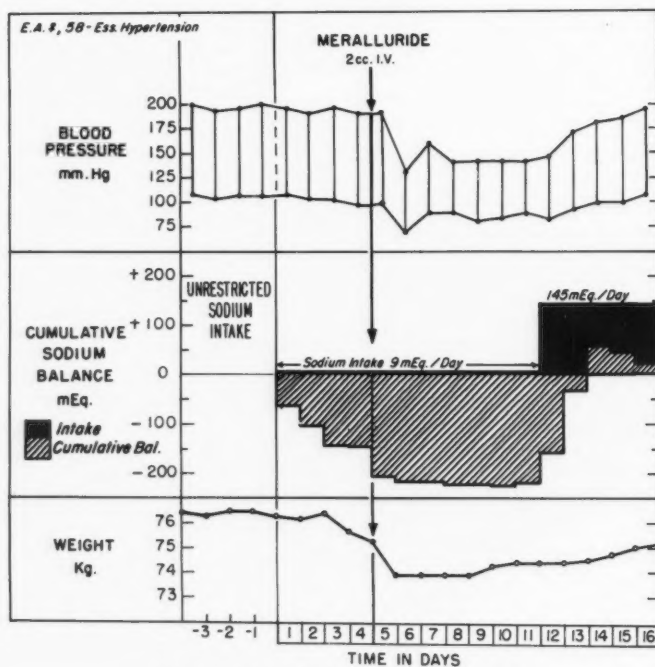
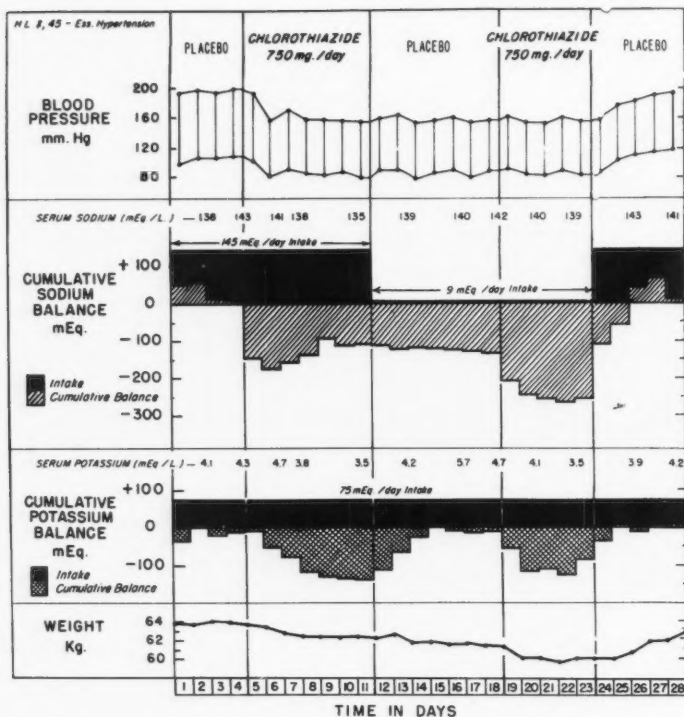
During a daily intake of 145 mEq. of sodium and 75 mEq. of potassium, chlorothiazide in an oral dose of 250 mg. 3 times a day produced a maximal cumulative negative balance of 170 mEq. of sodium and 136 mEq. of potassium. Accompanying the decreases in body sodium and potassium there was an appreciable reduction in blood pressure which appeared 25 hours after the start of chlorothiazide therapy. The losses in body sodium occurred during the first 2 days of treatment and were greatest on the first day of chloro-

thiazide administration. The losses of body potassium occurred gradually over a period of 5 days. As chlorothiazide was continued, the cumulative negative sodium balance rose toward normal, 62 to 81 mEq., but without an accompanying increase in the blood pressure.

When chlorothiazide was withdrawn and simultaneously the daily intake of sodium reduced to 9 mEq. on the twelfth metabolic day, the blood pressure did not rise but remained at the previous level of reduction. During this period the negative sodium balance previously caused by chlorothiazide persisted but the cumulative negative balance of potassium disappeared.

Following the reinstitution of chlorothiazide during the sodium restricted diet on the nineteenth metabolic day additional losses of body sodium and potassium occurred without a further reduction in blood pressure.

In general, changes in serum potassium varied in the same direction as those in the potassium balance, whereas changes in serum sodium were slight and did not necessarily accompany those in the cumulative sodium balance.



Figs. 1 and 2. (See legend opposite page.)

After withdrawing chlorothiazide and increasing the daily sodium intake to 145 mEq., the blood pressure increased to the pretreatment level while sodium and potassium balances returned to or above control values.

**Balance Study 2.** The effects of intravenous chlorothiazide on the blood pressure and sodium balance in subject, M.L., with essential hypertension are shown in table 2.

During a reduced sodium intake of 9 mEq. per day a cumulative negative sodium balance of 138 mEq. resulted without an appreciable change in the blood pressure. An intravenous injection of 1 Gm. of chlorothiazide on the sixth metabolic day was followed by a further sodium loss of 58 mEq. as well as a decrease in blood pressure. The reduction in blood pressure, which occurred 18 hours after the injection of chlorothiazide, persisted for 6 days along with a cumulative negative sodium balance of 149 to 196 mEq. during continued sodium restriction. After the daily sodium intake was increased to 145 mEq. on the thirteenth metabolic day, the sodium balance returned to and above control values while the blood pressure rose to pretreatment levels.

**Balance Study 3.** The effects of a parenteral mercurial diuretic on the blood pressure and sodium balance in subject, E.A., with essential hypertension are illustrated in figure 2.

After the sodium intake was restricted to 9 mEq. per day a cumulative negative sodium balance of 146 mEq. developed without a striking change in blood pressure. On the fifth metabolic day, 20 hours following the intravenous injection of meralluride, a marked reduction in blood pressure occurred together with an increase of 63 mEq. in the cumulative negative sodium balance. The hypotensive effect of meralluride like that of chloro-

thiazide persisted during the maintenance of sodium restriction and a negative sodium balance. However, when the daily intake of sodium was increased to 145 mEq. on the twelfth metabolic day, both the blood pressure and sodium balance returned to or above the control levels.

In repeating the same type of experiment in subject R.D. with essential hypertension (table 3) similar results were obtained. The hypotensive effect of intravenous mercapto-merin was associated with a cumulative negative sodium balance of 169 mEq. It persisted until the negative sodium balance, which was maintained by sodium restriction, reverted to and above control values following an increase of the sodium intake to 145 mEq. per day.

**Balance Study 4.** The effects of chlorothiazide and a mercurial diuretic on the blood pressure and sodium balance in a splanchnicectomized subject, C.L., with renal hypertension are shown in figure 3.

During a reduced daily sodium intake of 77 mEq. the maximal reductions in blood pressure and losses of sodium occurred during the first 2 days of chlorothiazide treatment. However, the initial fall in blood pressure of 25/20 mm. Hg appeared 4 hours after the start of chlorothiazide and was associated with a net sodium loss of 48 mEq. As chlorothiazide was continued, the cumulative negative sodium balance moderated from 226 to 165 mEq. but then returned toward the greater negative values. During these changes in sodium balance the hypotensive effect of chlorothiazide was not strikingly altered.

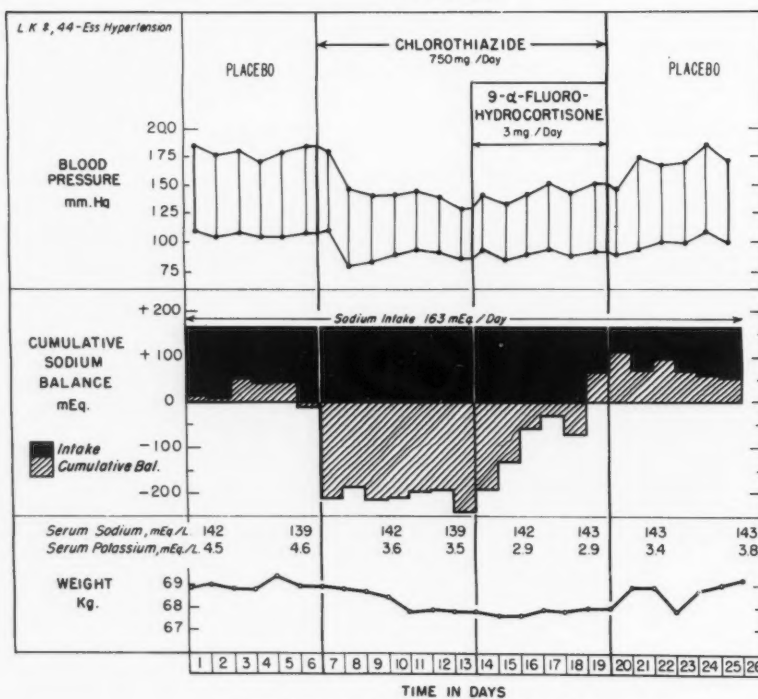
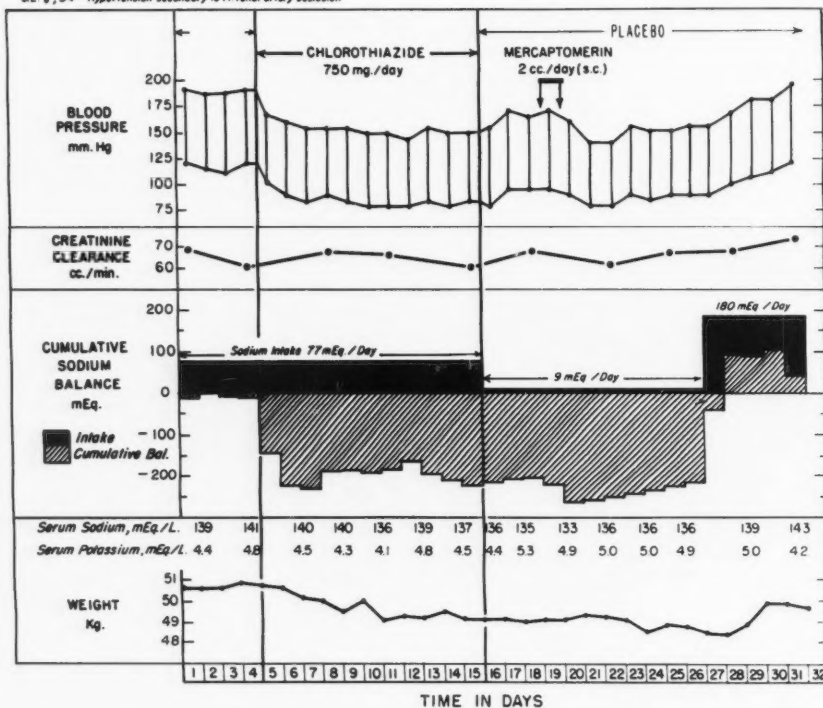
When chlorothiazide was withdrawn while the daily sodium intake was simultaneously reduced to 9 mEq. per day on the sixteenth

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FIG. 1 *Top.* Study 1: Oral chlorothiazide in a subject with essential hypertension. In each balance figure, the blood pressure which is plotted daily is the average value of 6 or more determinations. The daily intake of sodium or potassium is measured upward from the zero baseline. The cumulative negative sodium or potassium balance is shown by a *hatched* or *cross-hatched* area below the zero baseline. The cumulative positive sodium or potassium balance is plotted above the zero baseline. Weight in kilograms is shown at the beginning of each balance day.

FIG. 2 *Bottom.* Study 3: Intravenous meralluride in a subject with essential hypertension.

C.L. #, 54 - Hypertension secondary to renal artery occlusion



FIGS. 3 and 4. (See legend opposite page.)

metabolic day, the cumulative negative sodium balance continued at about the same level but the blood pressure, though still reduced, showed a slight rise.

Mercaptopmerin, which was administered parenterally during the restricted sodium intake on the nineteenth and twentieth metabolic days, produced an additional net sodium loss of 63 mEq. and a further reduction in blood pressure. The hypotensive effect of mercaptopmerin appeared to last for about 48 hours after the administration of the drug.

During the period of negative sodium balance there were no striking reductions in the creatinine clearance or in the serum potassium although there was a slight reduction in the serum sodium.

After all drugs were withdrawn and the daily intake of sodium was increased to 180 mEq., the blood pressure increased to the pretreatment values and the sodium balance returned to and above the control levels.

In subject E.M. with essential hypertension and previous splanchnicectomy (table 4) the onset of the hypotensive action of oral chlorothiazide during a daily sodium intake of 60 mEq. also occurred 4 hours after the administration of the drug and was associated with a net sodium loss of 52 mEq. On continuing chlorothiazide but reducing the sodium intake to 9 mEq. on the eleventh metabolic day, an additional reduction in blood pressure and increase in cumulative negative sodium balance resulted.

**Balance Study 5.** The effects of 9- $\alpha$ -fluorohydrocortisone on the natriuretic and hypotensive actions of chlorothiazide in subject, L.K., with essential hypertension are shown in figure 4.

During a daily intake of 163 mEq. of sodium the control blood pressure averaged 80/105 mm. Hg. After chlorothiazide was given on the seventh metabolic day the blood pressure decreased by an average of 37/15 mm. Hg and the net loss of sodium varied from

187 to 243 mEq. On the fourteenth metabolic day 9- $\alpha$ -fluorohydrocortisone in a daily dosage of 3 mg. was added to chlorothiazide. During the 6 days of steroid administration the cumulative negative sodium balance that followed chlorothiazide administration disappeared and sodium balance became positive as compared with control values, but the blood pressure increased only slightly and remained below control levels. Weight and serum sodium also did not change strikingly during this period whereas serum potassium decreased. After fluorohydrocortisone and chlorothiazide were both withdrawn, the blood pressure and weight rose to the control values while the net positive sodium balance, which increased initially, returned towards zero.

Similar experiments were repeated in subjects H.W. (table 5) and R.D. (fig. 5) with essential hypertension. In these subjects the hypotensive action of chlorothiazide after the addition of fluorohydrocortisone also persisted in the absence of a negative sodium balance. Although the blood pressure in subject R.D. rose as body sodium increased to and above control values following the administration of fluorohydrocortisone, it did not return to the pretreatment levels. In both of these subjects, as in subject L.K., the sodium retention following the administration of fluorohydrocortisone during chlorothiazide therapy was not accompanied by a noticeable increase in weight.

**Balance Study 6.** The effects of SC-8109, 3-(3-oxo-17  $\beta$ -hydroxy-19-nor-4-androsten-17- $\alpha$ -yl) propionic acid lactone, on the diuretic and hypotensive actions of chlorothiazide in subject R.D. with essential hypertension are shown in figure 5.

The effects of SC-8109, a "steroidal antagonist,"<sup>18, 19</sup> on the actions of chlorothiazide were studied because of the possibility that an increased excretion of aldosterone might account for the absence of a continued natri-

FIG. 3 *Top.* Study 4: Chlorothiazide and a mercurial diuretic in a subject with renal hypertension and splanchnicectomy.

FIG. 4 *Bottom.* Study 5: 9- $\alpha$ -fluorohydrocortisone in a subject with essential hypertension treated with chlorothiazide.

TABLE 3.—*Intravenous Mercaptomerin in Hypertensive Subject, R.D., Age 45 (Study 3)*

| Balance day | Drugs                                     | Average blood pressure (mm. Hg) | Weight (Kg.) | Sodium intake (mEq./day) | Urinary sodium excretion (mEq./day) | Daily sodium balance (mEq./day) | Cumulative sodium balance (mEq.) |
|-------------|---|---------------------------------|--------------|--------------------------|-------------------------------------|---------------------------------|----------------------------------|
| 1           | Oral placebo                              | 184/109                         | 54.0         | 9                        | 26                                  | -17                             | -17                              |
| 2           | Oral placebo                              | 185/108                         | 53.7         | 9                        | 11                                  | -2                              | -19                              |
| 3           | Oral placebo                              | 188/113                         | 53.5         | 9                        | 9                                   | 0                               | -19                              |
| 4           | Oral placebo                              | 186/110                         | 53.4         | 9                        | 7                                   | +2                              | -17                              |
| 5           | Oral placebo                              | 187/112                         | 53.2         | 9                        | 14                                  | -5                              | -22                              |
| 6           | Mercaptomerin 2 ml. I.V. and Oral placebo | 185/110                         | 53.5         | 9                        | 156                                 | -147                            | -169                             |
| 7           | Oral placebo                              | 152/94                          | 52.0         | 9                        | 2                                   | +7                              | -162                             |
| 8           | Oral placebo                              | 148/98                          | 52.0         | 9                        | 1                                   | +8                              | -154                             |
| 9           | Oral placebo                              | 150/95                          | 52.2         | 9                        | 1                                   | +8                              | -146                             |
| 10          | Oral placebo                              | 143/94                          | 52.3         | 9                        | 1                                   | +8                              | -138                             |
| 11          | Oral placebo                              | 151/99                          | 52.2         | 9                        | 1                                   | +8                              | -130                             |
| 12          | Oral placebo                              | 147/96                          | 52.2         | 145                      | 3                                   | +142                            | +12                              |
| 13          | Oral placebo                              | 152/97                          | 53.1         | 145                      | 86                                  | +59                             | +71                              |
| 14          | Oral placebo                              | 172/102                         | 53.3         | 145                      | 136                                 | +9                              | +80                              |
| 15          | Oral placebo                              | 184/112                         | 53.6         | 145                      | 162                                 | -17                             | +63                              |
| 16          | Oral placebo                              | 187/112                         | 53.4         | 145                      | 167                                 | -22                             | +41                              |

TABLE 4.—*Oral Chlorothiazide in Splanchicectomized Hypertensive Patient, E.M., Age 41 (Study 4)*

| Balance day | Drugs                      | Average blood pressure (mm. Hg) | Weight (Kg.) | Sodium intake (mEq./day) | Urinary sodium excretion (mEq./day) | Daily sodium balance (mEq./day) | Cumulative sodium balance (mEq.) |
|-------------|----------------------------|---------------------------------|--------------|--------------------------|-------------------------------------|---------------------------------|----------------------------------|
| 1           | Placebo                    | 212/138                         | 72.6         | 60                       | 49                                  | +11                             | +11                              |
| 2           | Placebo                    | 209/133                         | 72.6         | 60                       | 35                                  | +25                             | +36                              |
| 3           | Placebo                    | 208/136                         | 73.0         | 60                       | 48                                  | +12                             | +48                              |
| 4           | Placebo                    | 211/135                         | 73.2         | 60                       | 62                                  | -2                              | +46                              |
| 5           | Chlorothiazide 750 mg./day | 184/122                         | 73.5         | 60                       | 261                                 | -201                            | -155                             |
| 6           | Chlorothiazide 750 mg./day | 167/112                         | 73.3         | 60                       | 134                                 | -74                             | -229                             |
| 7           | Chlorothiazide 750 mg./day | 170/113                         | 71.3         | 60                       | 75                                  | -15                             | -244                             |
| 8           | Chlorothiazide 750 mg./day | 168/108                         | 71.3         | 60                       | 46                                  | +14                             | -230                             |
| 9           | Chlorothiazide 750 mg./day | 167/109                         | 71.4         | 60                       | 72                                  | -12                             | -242                             |
| 10          | Chlorothiazide 750 mg./day | 169/110                         | 71.2         | 60                       | 39                                  | +21                             | -221                             |
| 11          | Chlorothiazide 750 mg./day | 156/92                          | 70.4         | 9                        | 37                                  | -28                             | -249                             |
| 12          | Chlorothiazide 750 mg./day | 152/90                          | 70.7         | 9                        | 19                                  | -10                             | -259                             |
| 13          | Chlorothiazide 750 mg./day | 149/94                          | 70.5         | 9                        | 23                                  | -14                             | -273                             |
| 14          | Chlorothiazide 750 mg./day | 150/92                          | 70.6         | 9                        | 14                                  | -5                              | -278                             |
| 15          | Placebo                    | 172/110                         | 71.5         | 145                      | 3                                   | +142                            | -136                             |
| 16          | Placebo                    | 196/132                         | 72.4         | 145                      | 5                                   | +140                            | +4                               |
| 17          | Placebo                    | 206/135                         | 72.9         | 145                      | 63                                  | +82                             | +86                              |
| 18          | Placebo                    | 209/136                         | 72.6         | 145                      | 186                                 | -41                             | +45                              |

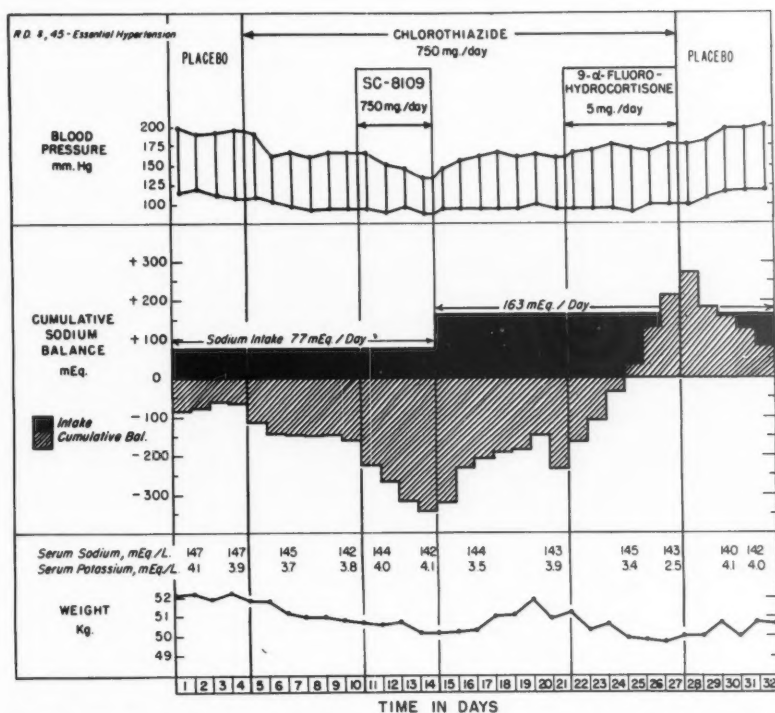


Fig. 5. Study 6: SC-8109, a steroidal lactone, and 9- $\alpha$ -fluorohydrocortisone in a subject with essential hypertension treated with chlorothiazide.

uretic effect of chlorothiazide and for the excess retention of sodium after the withdrawal of chlorothiazide.

On the eleventh metabolic day SC-8109 was added to chlorothiazide during a daily intake of 77 mEq. of sodium. At this time the net loss of sodium was 161 mEq. and no further reductions in body sodium and blood pressure were being produced by chlorothiazide. SC-8109 given in a daily dose of 750 mg. in combination with chlorothiazide for 4 days produced an additional loss of 181 mEq. of sodium and a decrease in blood pressure of 5/10 mm. Hg. During this period there was slight increase in serum potassium without an appreciable change in serum sodium. After withdrawing SC-8109 and increasing the daily intake of sodium to 163 mEq. on the fifteenth metabolic day while continuing chlorothiazide, the cumulative negative sodium balance de-

creased and the blood pressure increased to the levels that existed before the administration of SC-8109. The remaining part of the experiment was described in study 5.

#### DISCUSSION

Chlorothiazide or parenteral mercurial diuretics apparently exerted a hypotensive action in arterial hypertension during a daily sodium intake of 9 mEq. to 214 mEq. The reductions in blood pressure following the administration of these agents were usually associated with a cumulative negative sodium balance of 150 to 200 mEq. but occurred in splanchnicectomized hypertensive subjects during a net sodium loss as little as 50 mEq. The continued reduction in blood pressure after withdrawing the diuretic agents and restricting sodium intake to 9 mEq. per day was also associated with a continued negative

TABLE 5.—*Oral Chlorothiazide and 9- $\alpha$ -Fluorohydrocortisone in Hypertensive Subject, H.W., Age 34 (Study 5)*

| Balance day | Drugs  | Average blood pressure (mm. Hg) | Weight (Kg.) | Sodium intake (mEq./day) | Urinary sodium excretion (mEq./day) | Daily sodium balance (mEq./day) | Cumulative sodium balance (mEq.) |
|-------------|--|---------------------------------|--------------|--------------------------|-------------------------------------|---------------------------------|----------------------------------|
| 1           | Placebo  | 194/104                         | 91.4         | 214                      | 208                                 | +6                              | +6                               |
| 2           | Placebo  | 198/107                         | 91.7         | 214                      | 200                                 | +14                             | +20                              |
| 3           | Placebo  | 196/110                         | 91.5         | 214                      | 195                                 | +19                             | +39                              |
| 4           | Placebo  | 197/110                         | 91.5         | 214                      | 216                                 | -2                              | +37                              |
| 5           | Chlorothiazide 375 mg./day                         | 195/108                         | 90.6         | 214                      | 395                                 | -181                            | -144                             |
| 6           | Chlorothiazide 375 mg./day                         | 172/102                         | 90.2         | 214                      | 307                                 | -93                             | -237                             |
| 7           | Chlorothiazide 375 mg./day                         | 172/100                         | 90.0         | 214                      | 166                                 | +48                             | -189                             |
| 8           | Chlorothiazide 375 mg./day                         | 170/100                         | 90.1         | 214                      | 190                                 | +24                             | -165                             |
| 9           | Chlorothiazide 375 mg./day                         | 174/104                         | 89.3         | 214                      | 236                                 | -22                             | -187                             |
| 10          | Chlorothiazide 375 mg./day                         | 175/105                         | 89.0         | 214                      | 216                                 | -2                              | -189                             |
| 11          | Chlorothiazide 750 mg./day                         | 173/98                          | 88.5         | 214                      | 241                                 | -27                             | -216                             |
| 12          | Chlorothiazide 750 mg./day                         | 165/95                          | 88.0         | 214                      | 272                                 | -58                             | -274                             |
| 13          | Chlorothiazide 750 mg./day                         | 158/95                          | 88.5         | 214                      | 185                                 | +29                             | -245                             |
| 14          | Chlorothiazide 750 mg./day                         | 152/92                          | 87.2         | 214                      | 242                                 | -28                             | -273                             |
| 15          | Chlorothiazide—750 mg./day<br>+ Fluoro.*—5 mg./day | 146/92                          | 87.6         | 214                      | 174                                 | +40                             | -233                             |
| 16          | Chlorothiazide—750 mg./day<br>+ Fluoro.*—5 mg./day | 155/90                          | 88.1         | 214                      | 143                                 | +71                             | -162                             |
| 17          | Chlorothiazide—750 mg./day<br>+ Fluoro.*—5 mg./day | 152/94                          | 88.1         | 214                      | 152                                 | +62                             | -100                             |
| 18          | Chlorothiazide—750 mg./day<br>+ Fluoro.*—5 mg./day | 165/93                          | 88.2         | 214                      | 158                                 | +56                             | -44                              |
| 19          | Chlorothiazide—750 mg./day<br>+ Fluoro.*—5 mg./day | 155/92                          | 88.4         | 214                      | 194                                 | +20                             | -24                              |
| 20          | Chlorothiazide—750 mg./day<br>+ Fluoro.*—5 mg./day | 157/90                          | 88.1         | 214                      | 196                                 | +18                             | -6                               |
| 21          | Chlorothiazide—750 mg./day<br>+ Fluoro.*—5 mg./day | 162/92                          | 88.0         | 214                      | 193                                 | +21                             | +15                              |
| 22          | Placebo  | 160/90                          | 88.9         | 214                      | 116                                 | +98                             | +113                             |
| 23          | Placebo  | 168/97                          | 90.0         | 214                      | 209                                 | +5                              | +118                             |
| 24          | Placebo  | 178/106                         | 89.8         | 214                      | 251                                 | -37                             | +81                              |
| 25          | Placebo  | 183/107                         | 89.7         | 214                      | 243                                 | -29                             | +52                              |
| 26          | Placebo  | 194/110                         | 89.8         | 214                      | 233                                 | -19                             | +33                              |
| 27          | Placebo  | 197/112                         | 90.1         | 214                      | 209                                 | +5                              | +38                              |

\*Fluoro. = 9- $\alpha$ -fluorohydrocortisone.

sodium balance but not with a negative potassium balance. It seems unlikely that the continued reduction in blood pressure during this period was due to a reduced sodium intake per se, since salt restriction prior to the addition of the diuretics affected the blood pressure only slightly.

Although a reduction in body sodium may be capable of maintaining the hypotensive

effect of chlorothiazide and mercurial diuretics, the balance studies in which fluorohydrocortisone was added to chlorothiazide indicate that sodium depletion from the body may not be the sole cause of the antihypertensive action of these compounds. In these studies it was found that chlorothiazide exerted a hypotensive action in the absence of a negative sodium balance. However, the increase in blood

pressure, although not to pretreatment values following the addition of fluorohydrocortisone in 2 of 3 experimental subjects, suggests that a reduction in body sodium may potentiate as well as perpetuate the antihypertensive effect of chlorothiazide. Collateral studies also indicate that chlorothiazide given alone for prolonged periods may exhibit a hypotensive effect without an accompanying decrease in body sodium or potassium.<sup>9, 12, 13</sup> However, these as well as the present findings do not exclude local tissue shifts of electrolytes or changes in fluid volume as factors operating in the hypotensive action of chlorothiazide.

The observation that further reductions in blood pressure and body sodium were produced by the addition of SC-8109, a "steroidal antagonist,"<sup>18, 19</sup> to the chlorothiazide treatment is consistent with the notion that an increase in aldosterone activity may occur during the administration of chlorothiazide to counteract the natriuretic and possibly some of the hypotensive effects of chlorothiazide. However, these findings do not exclude a nonspecific effect of SC-8109 on salt excretion and blood pressure. It is noteworthy that an increased aldosterone excretion has been reported to occur following the administration of mercurial diuretics.<sup>20, 21</sup> The stimulus for an augmented aldosterone activity might be a reduced body sodium or a contracted blood volume (or both) caused initially by chlorothiazide or mercurial diuretics.

Chlorothiazide and mercurial diuretics appear to have a different antihypertensive action in patients with arterial hypertension than in normotensive subjects in whom they have no demonstrable hypotensive action. It is therefore possible that chlorothiazide and mercurials may operate similarly against some pressor mechanism. Since the antihypertensive effect of these compounds appears to be augmented and maintained by but not wholly dependent upon a reduction in total body sodium, it is conceivable that such an arterial pressor mechanism may be suppressed during the administration of chlorothiazide and mercurials with or without an accompanying

change in body sodium and reactivated following the withdrawal of these agents only when body sodium is at an optimum level. Preliminary observations<sup>13</sup> which suggested that chlorothiazide might reduce blood pressure by depressing the serum renin content, have not been confirmed.

#### SUMMARY

During a controlled sodium intake of 9 to 214 mEq. per day, chlorothiazide and parenteral mercurial diuretics produced a hypotensive effect in hypertensive patients that was associated with a negative sodium and potassium balance. The hypotensive action of these compounds, which was maintained after their withdrawal by restricting sodium intake, was also associated with a negative sodium but not a negative potassium balance. However, experiments in which fluorohydrocortisone was added to chlorothiazide indicated that chlorothiazide is capable of maintaining a lowered blood pressure in the presence of an unreduced body sodium. The natriuretic and hypotensive effects of chlorothiazide were increased by the addition of SC-8109, a steroidal lactone, to chlorothiazide. The findings that chlorothiazide and parenteral mercurial diuretics have a hypotensive action in subjects with arterial hypertension but not in normal individuals suggest that these compounds may operate similarly against some arterial pressor mechanism.

#### SUMMARY IN INTERLINGUA

Durante un regulate ingestion diurne de 9 a 214 mEq. de natrium, chlorothiazido e mercuriales parenteral produceva un effecto hypotensive in patinetes hypertensive, associate con un balancia negative de natrium e de kalium. Le action hypotensive de iste compositos, mantene post lor discontinuation per un restriction del ingestion de natrium, esseva etiam associate con un balancia negative de natrium sed non con un balancia negative de kalium. Tamen, experimentos in que fluorohydrocortisona esseva addite al chlorothiazido indicava que chlorothiazido es capace de mantener un reduceite tension de sanguine in

le presentia de non-reducite concentraciones de natrium in le corpore. Le effectos natriuretice e hypotensive de chlorothiazido esseva augmentate per le addition de SC-8109 (un lactona steroidal) al chlorothiazido. Le observation que chlorothiazido e diureticos mercurial in administrationes parenteral ha un effecto hypotensive in subjectos con hypertension arterial sed non in subjectos normal suggere que iste compositos age similemente contra certe mecanismos arterio-pressorii.

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# Mitral Incompetence Caused by Disease of the Mural Cusp

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LEO R. RADIGAN, M.D., F.A.C.S.

Mitral regurgitation can be caused by one or a combination of different anatomic lesions. Because of this the authors believe that the surgeon can be aided if the type of defect is known preoperatively. The present study of 240 patients with disease of the mitral valve revealed a significant number whose disease was limited to the mural cusp. Criteria for the bedside diagnosis of this type of mitral regurgitation are presented.

**W**ITHIN the past few years there have been several reports of surgical procedures for the correction of mitral regurgitation. When, however, one studies the autopsy specimens of patients who had rheumatic mitral valve incompetence, it seems unlikely that any one operation short of complete replacement of the mitral valve would adequately repair the variety of anatomic defects that can exist. Brock,<sup>1</sup> has investigated the anatomy of these lesions and has described shortening of one or both mitral cusps, rupture or shortening of the musculotendinous mechanism, stiffness of the cusp margins preventing closure, and dilatation of the atrioventricular ring. If the surgeon could be relatively certain which of the anatomic lesions was present, he could better determine the operative procedure best suited to correct that defect. The present study is an attempt to establish criteria for the diagnosis of one form of mitral incompetence.

When rheumatic valvulitis primarily affects the mural leaflet, it can reduce the size or mobility of the cusp in such a way that the relatively healthy aortic leaflet cannot close against it in systole. We believe this form of mitral regurgitation has specific diagnostic clinical features that can be recognized at the bedside.

## MATERIALS AND METHODS

Two hundred and forty patients with mitral valve disease were examined by one of us (P.N.) in the General Infirmary at Leeds during 1957 and 1958. Twenty-nine formed a distinct group,

From the Cardiac and Thoracic Surgery Clinics of the Leeds General Infirmary, Leeds, England, and the Veterans Administration Hospital, Indianapolis, Ind.

having in common the unusual combination of mitral incompetence with distinct mitral closing and opening snaps. In some of these 29 patients the incompetence was extreme, and opening and closing snaps persisted in the presence of left ventricular hypertrophy and the third heart sound of rapid early diastolic ventricular filling. In others, adhesion between the diseased mural cusp and the relatively healthy aortic leaflet had so reduced the size of the orifice that regurgitation appeared to be less important than stenosis and was clinically evident only in a pansystolic apical murmur. Eleven of these patients were sufficiently disabled to necessitate valvulotomy (G.H.W. and L.R.R.), which made digital examination of the mitral valve possible.

In each, the aortic cusp was found to be relatively healthy, but the mural cusp was diseased and permitted regurgitation. The operators' descriptions of the mitral valve in this group of 11 cases are listed in table 1. The important clinical and hemodynamic features observed in these same patients are tabulated in table 2, and one patient is reported in detail. Systemic blood pressures were obtained with a sphygmomanometer in patients supine and resting. The electrocardiographic criteria for the diagnosis of ventricular hypertrophy were those of Sokolow and Lyon.<sup>2,3</sup> A phonocardiograph with a logarithmic frequency response was used to record sounds from the pulmonary area and apex.

Left atrial and pulmonary artery pressure pulses were obtained by needle puncture through a bronchoscope, using a modification of the technique devised by Allison and Linden.<sup>4</sup> The zero reference point used was the sternal angle. All records were taken during an expiratory pause.

## CASE REPORT

*Case 8, E.H., female, age 42 years.* Apart from chorea at 13 years, there was no illness until 1943, when breathlessness on effort and fatigue were first noticed. The severity of the symptoms altered little until early in 1956, when dyspnea grew troublesome. In the summer of 1957 she had to

give up work because traveling and climbing stairs had become difficult. At the time of the present examination, in July 1958, dyspnea and fatigue prevented her from walking more than 25 yards without resting. It was necessary for her to sleep propped up in bed. There had been no hemoptysis and no edema. There was no evidence of disease other than the cardiac disorder.

Examination showed a tall lean patient with malar cyanosis and cold, blue hands but no central cyanosis. The jugular venous pressure was normal. There was no enlargement of the liver or edema. The radial pulse was irregular but of normal quality. The blood pressure was 140/90. Her apex beat was palpable in the seventh left intercostal space in the midaxillary line. The cardiac impulse was a well-marked apical thrust of left ventricular hypertrophy, and a parasternal heave of right ventricular enlargement. The pulmonary valve closure was easily palpable. The mitral first sound was accentuated and followed by a loud pansystolic murmur, second sound, opening snap, third sound, and short diastolic murmur. A quiet pansystolic murmur at the left sternal border was considered to be conducted from the mitral area. The second sound in the pulmonary area split normally during inspiration, and the sound of pulmonary valve closure was accentuated. There was no evidence of aortic valvular disease.

The lungs, abdomen, and nervous system were normal. Blood count and sedimentation rate were normal.

The electrocardiogram showed atrial fibrillation, vertical heart position, and left ventricular hypertrophy (fig. 1). The phonocardiogram confirmed the auscultatory findings (fig. 2). X-ray examination (fig. 3) showed enlargement of the ventricles, small aortic knuckle, prominence of the hilar vessels, and pulmonary venous congestion. Horizontal lines were probably present, but not distinct. The left atrium was markedly enlarged, and formed part of the right border of the heart in the posteroanterior film. Eighteen months before the present examination the left atrial and pulmonary artery pressures (fig. 4) were recorded: Pulmonary artery mean pressure, 28 mm. Hg; mean left atrial pressure, 15.5 mm. Hg; left atrial pressure at "v", 28.4 mm. Hg; Ry/v factor,<sup>5</sup> 3.6; V/M factor,<sup>6</sup> 1.86.

Operation was performed on July 10, 1958. Using the phonocardiograph to provide an extracorporeal circulation of 1.7 L./M.<sup>2</sup>/minute at a body temperature of 33.5 C., the left atrium was opened widely and the mitral valve examined. The lumen measured 2.5 cm. in diameter. The aortic leaflet was mobile and only slightly thickened. The mural cusp was thickened, rolled upon itself, and tethered down by shortened chordae

TABLE 1.—Condition of the Mitral Valve at Cardiotomy

| Case    | Remarks  |
|---------|--|
| 1 W.F.  | Orifice approximately 2 cm. in diameter. Posterior commissure thickly fibrosed. Aortic leaflet reasonably healthy, and moving a great deal. Mural cusp immobile and thickened. Regurgitant stream increased by division of the posterior commissure. |
| 2 I.S.  | Orifice approximately 1.5 cm. in diameter. Aortic leaflet mobile. Mural cusp completely fixed. Regurgitant jet increased by division of the anterior commissure.   |
| 3 K.S.  | Orifice approximately 3.0 cm. in diameter. Gross regurgitant stream. Mural cusp thickened, rolled upon itself, and immobile. Aortic cusp appeared undiseased and mobile, but could not meet the retracted mural cusp.                                |
| 4 E.M.  | Orifice approximately 2.5 cm. in diameter. Gross regurgitant stream. Aortic leaflet mobile, but unable to meet the diseased mural cusp.  |
| 5 H.L.  | Orifice approximately 1.2 cm. in diameter. Regurgitant jet. Aortic leaflet almost undiseased and freely mobile. Mural cusp grossly diseased, thickened, and immobile.  |
| 6 M.J.  | Orifice approximately 2.5 cm. in diameter. Regurgitant stream. Aortic leaflet hardly diseased and very mobile. Mural cusp immobile, thickened, and rolled upon itself so that the aortic leaflet could not meet it.                                  |
| 7 M.L.  | Orifice approximately 3 cm. in diameter. Regurgitant jet. Aortic leaflet freely mobile and apparently undiseased. Mural cusp greatly thickened and rolled upon itself so that it could not be met by the aortic leaflet.                             |
| 8 E.H.  | Orifice approximately 2.5 cm. in diameter. Considerable regurgitant flow. Aortic leaflet pliant and mobile. Mural cusp thickened, rolled, immobile, and held to the ventricular wall by short thick chordae tendineae.                               |
| 9 L.S.  | Orifice approximately 1.5 cm. in diameter. Moderate regurgitant jet. Aortic leaflet full and mobile. Mural cusp rigid and immobile.  |
| 10 W.P. | Orifice approximately 2 cm. in diameter. Regurgitant stream. Aortic cusp pliant and mobile. Mural cusp shriveled and functionless.   |
| 11 A.B. | Orifice approximately 1.5 cm. in diameter. Regurgitant jet. Aortic cusp freely movable and ballooned normally. Its edge was thickened and fused at the lateral and medial commissures to a thickened narrow, and immobile mural cusp.                |

TABLE 2.—*Cardiographic and Hemodynamic Findings in Eleven Patients with Mural Cusp Disease*

| Patient | Rhythm  | Cardiographic |                              |                         | Hemodynamic                        |                                      |       |   |                                  |
|---------|---------|---------------|------------------------------|-------------------------|------------------------------------|--------------------------------------|-------|---|----------------------------------|
|         |         | Mitral P wave | Electrical position of heart | Ventricular hypertrophy | Mean left atrial pressure (mm. Hg) | Left atrial pressure at "V" (mm. Hg) | Ry/v* | Mean pulmonary artery pressure (mm. Hg) | Systemic blood pressure (mm. Hg) |
| 1       | W.F. SR | X             | Vertical                     | Left                    | 16                                 | 21                                   | 1.44  | 21                                      | 120/70                           |
| 2       | I.S. SR | X             | Vertical                     | ?                       | 15                                 | 22                                   | 3     | 32                                      | 135/80                           |
| 3       | K.S. AF | —             | Vertical                     | Left                    | 17                                 | 27.5                                 | 3.55  | 44                                      | 100/70                           |
| 4       | E.M. SR | X             | Vertical                     | Right                   | 33                                 | 45.5                                 | 2.25  | 60                                      | 120/80                           |
| 5       | H.L. AF | —             | Vertical                     | Left                    | 30                                 | 41.4                                 | 1.18  | 40                                      | 130/80                           |
| 6       | M.J. AF | —             | Intermediate                 | Left                    | 18.4                               | 22                                   | 2.64  | 30                                      | 140/80                           |
| 7       | M.L. AF | —             | Vertical                     | None                    | 20.6                               | 28                                   | 0.95  | —                                       | 100/70                           |
| 8       | E.H. AF | —             | Vertical                     | Left                    | 15.5                               | 28.5                                 | 3.6   | 28                                      | 140/90                           |
| 9       | L.S. SR | X             | Vertical                     | None                    | 19.5                               | 23                                   | 3.8   | —                                       | 140/80                           |
| 10      | W.P. SR | X             | Intermediate                 | None                    | —                                  | —                                    | —     | —                                       | 130/70                           |
| 11      | A.B. SR | X             | Vertical                     | None                    | 22                                 | 40                                   | 1.65  | —                                       | 120/70                           |

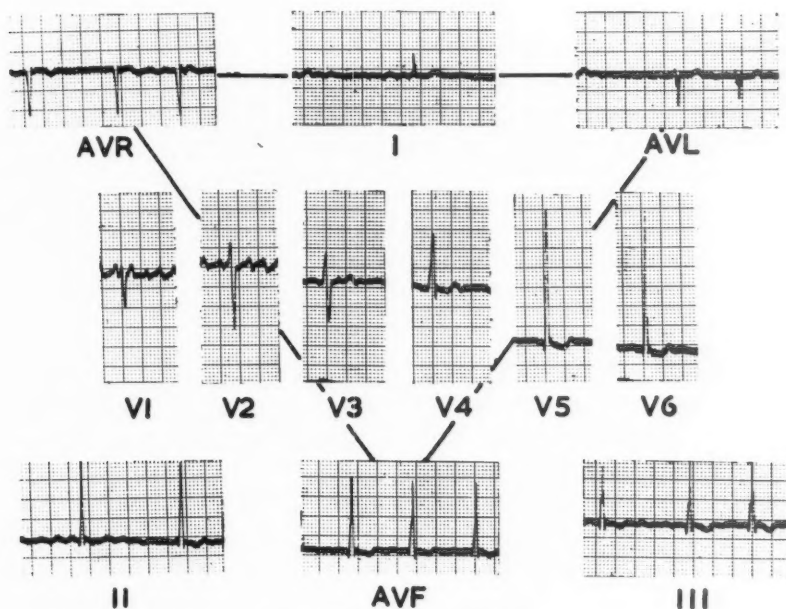
\*Owen and Wood.<sup>5</sup>

FIG. 1. Case 8, electrocardiogram.

andineae. Regurgitation occurred through the central and posterior parts of the lumen. The anterior commissure was obliterated. The anterior commissure was opened with scissors. Posterior regurgitation was reduced by the insertion of 2 pieces through the posterior part of the annulus. A piece of Ivalon sponge was then sutured to the mural cusp to form a cushion against which the

aortic leaflet could close. This patient made an uneventful recovery.

#### DISCUSSION

The patients in this study were carefully examined with particular reference to the physical signs of mitral closing and opening snaps, the pansystolic murmur of mitral re-

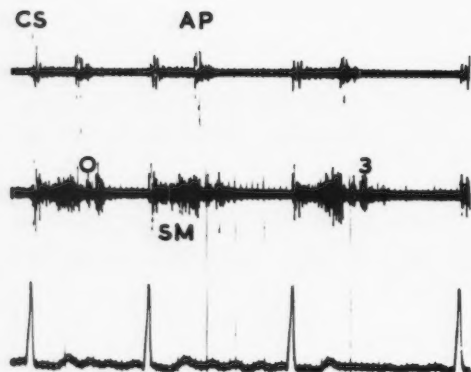


FIG. 2. High-frequency phonocardiogram. *Upper tracing*, pulmonary area; *middle tracing*, mitral area; *lower tracing*, electrocardiogram lead II; *CS*, closing snap of mitral valve; *A*, aortic valve closure; *P*, pulmonary valve closure; *O*, opening snap of mitral valve; *3*, third heart sound of rapid early diastolic ventricular filling; *SM*, pansystolic murmur of mitral regurgitation.

gurgitation, the third heart sound of rapid early diastolic ventricular filling, and the thrusting cardiac impulse of left ventricular hypertrophy. The criteria for the recognition of these signs are well established and have been reviewed by Wood.<sup>7</sup> In the cases we report, the closing snap or loud mitral first sound has contrasted strongly with the usually quiet first heart sound of mitral incompetence. By deduction it would thus seem that a quiet first sound would indicate fixed or destroyed mitral cusps.

The systolic murmur has been easily heard and in our patients has not been simulated by the ejection murmur of aortic stenosis. The only difficulty we have encountered has occurred in distinguishing between the pansystolic murmurs of mitral and tricuspid regurgitation in those patients with little or no left ventricular hypertrophy and in whom right ventricular enlargement has caused clockwise rotation of the heart.

The opening snap was readily audible in 10 of the 11 patients who were operated upon. In one it was recognized with difficulty because the mitral incompetence had shortened ventricular systole to such a degree that mitral valve opening nearly coincided with the

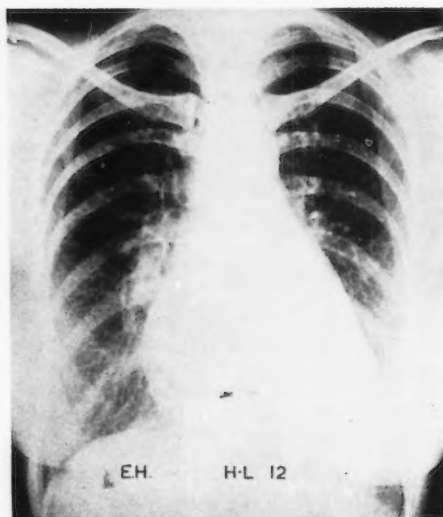


FIG. 3. Case 8, posteroanterior chest x-ray.

loud pulmonary valve closure. The third heart sound of rapid early diastolic ventricular filling must occur after the opening snap. Unlike the opening snap, this sound is of a low frequency and can rarely be heard at the pulmonary area. While it has been possible to record the third sound by phonocardiography, we have had difficulty in distinguishing it by auscultation within the short, loud, almost explosive diastolic murmur that has been present in some cases of severe mitral incompetence.

#### *Causation of Mitral Opening and Closing Snaps*

The importance of cusp mobility in the production of mitral opening and closing snaps was recognized when advances in cardiac surgery stimulated a close examination of the meaning of the physical signs in mitral valve disease.<sup>8</sup> Prior to this, it was considered that the presence of these snaps excluded gross incompetence. Recent reports, however, have described the occurrence of opening and closing snaps in patients with dominant regurgitation.<sup>9, 10</sup> In addition, Wood<sup>11</sup> and McDonald et al.<sup>12</sup> have heard the third sound of rapid early diastolic ventricular filling in patients with opening snaps.

All the patients who were operated upon in this series had mitral incompetence and, in some, this was the dominant lesion. All of them had opening or closing snaps, or both, and none of them had a mobile or effective mural cusp. It therefore seems clear that their opening and closing snaps must be caused by upward and downward movement of a mobile aortic cusp.

#### *Possible Clinical Course of Mural Cusp Disease and Surgical Considerations*

The mural cusp normally seals only a narrow crescent of the mitral orifice; so it is probable that regurgitation is slight in the early stages of its disease. Burchell and Edwards<sup>13</sup> have speculated upon the consequences of regurgitation in a case of the type we describe, and suggest that it leads to dilatation of the left atrium, which in turn causes posterior retraction of the mural cusp and increased regurgitation, and sets up a vicious circle that ends in gross incompetence and marked dilatation of the atrioventricular ring. If this view is correct it follows that there may be advantage in treating mural cusp disease when the defect is small and not too difficult to close with a prosthesis. We consider that there may be a second reason for operating at a relatively early stage of this disease, namely, the possibility that commissurotomy to free the aortic cusp may greatly increase regurgitant flow if dilatation of the atrioventricular ring has already occurred.

An approach to the treatment of mural cusp disease has already been made. Sakakariba<sup>14</sup> employed a sling to elevate the edge of the mural cusp after freeing the aortic cusp by commissurotomy. Making use of advances in the technic of extracorporeal circulation, Lillehei et al.,<sup>15</sup> and the present authors have sutured Ivalon sponge to the mural cusp to form a cushion against which the pliant and mobile aortic cusp can close in systole.

#### *Incidence of Mural Cusp Disease*

Only a relative idea of the incidence of mural cusp disease can be drawn at present. The characteristic physical signs were found

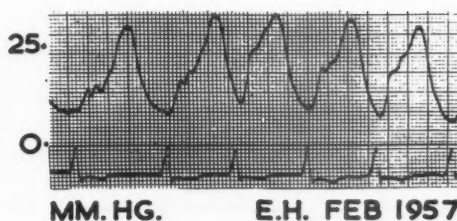


FIG. 4. Case 8, left atrial pressure curve.

in 29 (12 per cent) of a series of 240 patients with mitral valve disease examined by one observer in the Cardiological and Thoracic Surgical Clinics of a general hospital during 1957 and 1958. Most cases were referred for consideration of mitral valvulotomy and 120 had this operation performed. Only those patients in whom mitral valve disorder was the chief cardiac lesion were included in the series.

#### SUMMARY

A syndrome that has received little attention in the literature was present in 12 per cent of a series of 240 cases of mitral valve disease. The characteristic clinical feature was the presence of mitral opening and closing snaps in patients with mitral incompetence. The valve was examined at cardiectomy in the 11 cases reported, and the cause of regurgitation in each was disease of the mural cusp, the aortic leaflet being pliant and mobile.

Since none of the cases reported had an effective mural cusp, and since some had considerable regurgitation, it follows that mitral opening and closing snaps are produced by movement of the aortic leaflet.

It has been found possible at open heart operation to relieve the regurgitation of mural cusp disease by suturing a prosthesis to the mural cusp in such a way as to form a cushion against which the aortic leaflet can close in systole. It is suggested that the condition is best treated before serious dilatation of the mitral annulus occurs.

#### ACKNOWLEDGMENT

The authors wish to thank Dr. William Whitaker for his helpful advice and criticism.

## SUMMARIO IN INTERLINGUA

Un syndrome a que pauc attention es prestata in le litteratura esseva incontrate in 12 pro cento de un serie de 240 casos de morbo del valvula mitral. Le characteristic aspectu clinic esseva le presentia de clics de apertura e clauditura in patientes con incompetentia mitral. In le 11 casos hic reportate, le valvula esseva examine in cardiostomia, e le causa del regurgitation, in omne iste casos, esseva morbo del cuspidu mural—con plicabilitate e mobilitate del folio aortic.

Viste que in nulle del casos hic reportate il habeva un efficace cuspidu mural e que in certes il habeva considerabile grados de regurgitation, il seque que le clics de apertura e clauditura mitral es producite per movimientos del folio aortic.

Il se ha provate possibile alleviar, in operationes cardiacae aperte, le regurgitation de morbo de cuspidu mural per suturar un prothese al cuspidu mural de maniera a formar un cossino contra le qual le folio aortic pote effectuar un clauditura in systole. Es exprimate le opinion que le condition es a tractar preferibilemente ante que un serie dilatation del anulo mitral ha occurrite.

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## Influence of Some Vasoactive Drugs on Fibrinolytic Activity

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With the technical assistance of Louis G. Weisberg, B.S., and Gordon R. Gilbert, B.S.

The phenomenon of fibrinolysis in thromboembolic disease is of great importance. In this communication the authors present striking evidence of fibrinolysis induced by drugs.

A RECENTLY published tabulation<sup>1</sup> of simple organic compounds reported to induce some weak fibrinolytic activity includes only compounds known to influence vasomotion (procaine, epinephrine, diethylaminoethanol). Studies in our laboratory concerning the influence of vasomotor drugs on the clotting mechanism have resulted in the observation that intravenously administered nicotinic acid induces rather strong fibrinolytic activity.<sup>2</sup> This paper presents data on the influence of representative vasomotor drugs on the clotting mechanism, and particularly on fibrinolysis.

### METHODS

Rates of peripheral blood flow were measured in man in a constant temperature-constant humidity room by methods previously described.<sup>3</sup> Clotting tests included 1-stage prothrombin time (whole and diluted plasma),<sup>4</sup> recalcification time,<sup>5</sup> antithrombin activity<sup>6</sup> and fibrinolytic activity, both by test tube observation<sup>7</sup> and the coagulograph ("thromboelastograph" of Hartert).<sup>8,9</sup> Drugs studied in man included nicotinic acid (orally, intravenously, intramuscularly, and intra-arterially), nicotinamide (intravenously), calcium gluconate (intravenously), diethylaminoethanol (intravenously), histamine (intravenously), papaverine (intravenously and intra-arterially) and lidar (intra-arterially).

### RESULTS

*Nicotinic Acid.* In no experiment was there a significant alteration in any of the clotting tests performed except fibrinolysis. Following

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a single intravenous dose of nicotinic acid in man, marked fibrinolytic activity was noted, both by test tube observation and the coagulograph. The nicotinic acid flush was maximal during the period of injection. Fibrinolysis was not evident until several minutes after completion of the injection. Nicotinic acid in doses of 10 to 100 mg. was injected intravenously in 13 experiments, intra-arterially in 3, and intramuscularly in 2. In 17 of the 18 experiments, distinct fibrinolytic activity was noted without any significant alteration in the prothrombin complex as measured by a 1-stage technic, recalcification time, antithrombin activity, or heparin tolerance. Fibrinolytic activity was usually maximal about 5 to 20 minutes after injection and then became less intense but occasionally was still detectable after 1 to 2 hours. Figure 1 presents the coagulographs of 6 experiments in the same subject. Larger intravenous doses resulted not only in more rapid completion of lysis 20 minutes after injection but also in persistent lysis 1 hour after dosage. In 2 instances, the double-curve phenomenon on the coagulograph previously reported by Von Kaulia<sup>1</sup> was noted. The effect on blood flow to the lower extremity was studied in 6 of the intravenous and in the 3 intra-arterial experiments. In all 6 intravenous experiments, increases of flow rate were recorded, ranging from 64 to 290 per cent of the control values. In the 3 intra-arterial experiments, the flow rate increased by 250 and 97 per cent in 2, and decreased slightly in 1. All 3 showed distinct fibrinolysis.

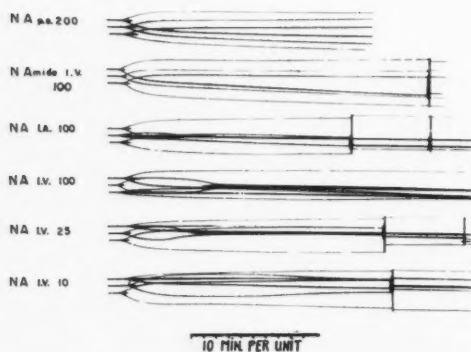


FIG. 1. Coagulograph patterns of plasma specimens from the same subject before (top curves), 20 minutes after (middle curves), and 1 hour after (bottom curves) single doses of nicotinic acid or nicotinamide as indicated to the left of each set of curves. Vertical lines, overnight interruptions of recordings.

The *in vitro* addition of nicotinic acid to plasma in concentrations of 0.05 to 500 mg./L. failed to induce any fibrinolytic activity. Oral administration of single doses of from 100 to 300 mg. in 11 subjects did not result in fibrinolysis in any of the experiments. In most instances, there was a distinct flush 10 to 20 minutes after oral administration, indicating that the drug was absorbed. The chronic oral administration of daily doses of 300 to 6,200 mg. for periods of from 1 to 25 weeks in 4 subjects also failed to yield any evidence of lysis.

The intravenous administration of nicotinic acid to dogs, guinea pigs, and rabbits failed to result in fibrinolysis as judged by the techniques described.

**Nicotinamide.** Since this substance has the same antipellagra activity as nicotinic acid (and is believed to be the essential form of this vitamin in important enzyme-cofactor systems), but is not vasoactive, its fibrinolytic effect was studied. Three of the subjects who had demonstrated marked fibrinolysis following nicotinic acid were given an identical dose of nicotinamide intravenously. No fibrinolytic phenomena resulted.

**Calcium Gluconate.** Since the intravenous injection of this substance results in a flush

similar to that following nicotinic acid, its effect on the clot was observed in 3 subjects. There was no evidence of fibrinolytic activity.

**Histamine.** Three patients given 3 mg. intra-arterially were observed to develop significant increases in blood flow rate (table 1) but failed to show any altered fibrinolytic activity.

**Papaverine.** This drug was administered intravenously in 2 experiments, and intra-arterially in 1 in doses of 30 to 45 mg., resulting in a distinct increase in rate of blood flow in the extremity. There was no activation of fibrinolysis.

**Ilidar.** In 3 experiments, 50 mg. infused intra-arterially resulted in an increase in blood flow in all instances. No fibrinolysis was induced.

**Diethylaminoethanol.** Although marked increase in blood flow was observed in all of 3 experiments, in only 1 was some weak fibrinolytic activity observed.

#### DISCUSSION

The capacity of parenterally administered nicotinic acid to induce fibrinolytic activity *in vivo* in man has been demonstrated. The mechanism of this phenomenon and the reason for its failure to develop in other species remain obscure. The absorption of orally administered nicotinic acid in man is well established and was confirmed in these studies by the observation of the flush in many subjects. Nevertheless, even the largest oral dose employed failed to induce fibrinolysis.

Since intravenously administered nicotinamide failed to activate fibrinolysis and also had no vasomotor activity, a relationship between vasodilatation and fibrinolytic activity was suspected. Nicotinic acid influences the superficial skin capillary bed as is evidenced by the flush. Contrary to common belief, this flush phenomenon is not necessarily accompanied by an elevation in skin temperature or a measurable increase in blood flow rate. Nicotinic acid does, however, affect the rate of blood flow to the lower limb, not correlated in time with the flush phenomenon. It was

TABLE 1.—*Effect of Vasomotor Drugs on Fibrinolytic Activity*

| Drug                 | Dose                       | Route of administration | Number of experiments | Effect on fibrinolytic activity  |                       |  |
|----------------------|----------------------------|-------------------------|-----------------------|----------------------------------|-----------------------|--|
|                      |                            |                         |                       | Coagulograph                     | Test tube             | Average per cent increase in blood flow rate |
| Nicotinic acid*      | 10 to 100 mg.              | I.V.                    | 13                    | Lysis in 12                      | Lysis in all          | 117  |
|                      | 100 mg.                    | I.A.                    | 3                     | Lysis in all                     | Lysis in all          | 107  |
|                      | 50 mg.                     | I.M.                    | 2                     | Lysis in all                     | Lysis in all          | —  |
|                      | 100 to 300 mg.             | Oral                    | 11                    | No lysis                         | No lysis              | —  |
|                      |                            |                         |                       |                                  |                       |  |
| Nicotinamide         | 100 mg.                    | I.V.                    | 3                     | No lysis                         | No lysis              | —  |
| Calcium gluconate    | 10 ml. of 10% solution     | I.V.                    | 3                     | No lysis                         | No lysis              | —  |
| Histamine            | 3 mg.                      | I.A.                    | 3                     | No lysis                         | No lysis              | 144  |
| Papaverine           | 45 mg.                     | I.V.                    | 2                     | No lysis                         | No lysis              | 94   |
|                      | 30 mg.                     | I.A.                    | 1                     | No lysis                         | No lysis              | 475  |
| Ilidar               | 50 mg. in 200 ml. infusion | I.A.                    | 3                     | No lysis                         | No lysis              | 110  |
| Diethylamino-ethanol | 50 ml. of 10% solution     | I.A.                    | 1                     | No lysis                         | No lysis              | 143  |
|                      |                            | I.V.                    | 2                     | Incomplete lysis in 1 experiment | Lysis in 1 experiment | 214  |

\*Tabulation includes only patients who had not previously received nicotinic acid by other routes.

therefore, thought necessary to look for a nicotinic acid-like fibrinolytic effect of other flush-inducing drugs as well as of drugs that increase rate of blood flow to a limb in the manner of nicotinic acid. Calcium gluconate, histamine, papaverine, and Ilidar all failed to induce fibrinolysis.

Experiments currently in progress indicate that orally administered nicotinic acid not only fails to induce fibrinolysis, but may alter the usual fibrinolytic response to subsequent intravenous doses.

#### SUMMARY

Parenterally administered nicotinic acid induces fibrinolytic activity in man. This response does not occur with a variety of other drugs capable of increasing rate of peripheral blood flow. Oral nicotinic acid and parenteral nicotinamide fail to induce fibrinolysis.

#### SUMMARIO IN INTERLINGUA

Acido nicotinic, administrate per via parenteral, induce activitate fibrinolytic in humanos. Iste responsa non occurre con un varietate de altere drogas capace a accelerar le fluxo de sanguine peripheric. Acido nicotinic per via oral e nicotinamindo per via parenteral non induce fibrinolyse.

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**Stevens, H.: Spontaneous Strokes in the Young.** *Ann. Int. Med.* 49:1022 (Nov.), 1958.

Data are presented on 30 healthy individuals aged 5½ to 45 years who sustained cerebrovascular accidents. The 2 large categories of strokes in the young were venous and arterial thrombosis. In healthy women, puerperal hemiplegia was the most common form of spontaneous stroke. It was characterized by the sudden onset of headache, convulsions, hemiplegia, or other focal neurologic signs during a previously healthy puerperal period. The episode occurred several hours to several weeks postpartum and was caused by cortical venous thrombosis. Twelve patients were reported with recovery in all, although minor neurologic sequelae persisted in 3 patients. Two other patients had similar findings during pregnancy; these were also thought to be caused by venous thrombosis. Arterial occlusion was thought to be the cause of strokes in the 16 other patients. Involvement of the carotid artery was often seen in strokes in the young. The cardinal sign of thrombosis of this vessel was hemiplegia. Contralateral headache was often present. Horner's syndrome and homonymous hemianopsia were frequent ocular signs of carotid artery thrombosis. The difficulty in distinguishing between middle cerebral and carotid artery thrombosis was discussed. Carotid arteriography was not recommended as a diagnostic procedure because of the hazard of precipitating or exacerbating a hemiplegia in an already susceptible patient. The cause of thrombosis in these patients was thought to be a solitary atheromatous plaque. No specific treatment was recommended, since prognosis is good in these patients.

KAYDEN

# Dietary Fat, Serum Cholesterol Levels and Incidence of Atherosclerosis in Delhi

By S. PADMAVATI, M.R.C.P., F.R.C.P.E., S. GUPTA, M.D., AND  
G. V. A. PANTULU, M.Sc.

Very little information is available about the incidence of coronary heart disease in India, or of factors considered responsible for it. In a previous paper, the incidence of atherosclerosis as judged by electrocardiogram, the fat intake, and serum cholesterol levels in 2 low-income groups (industrial and rural) in Delhi were investigated. These data in high-income groups in Delhi have now been studied and the results compared. There were considerable differences in the findings in the 2 groups.

**I**N A previous paper,<sup>1</sup> the values for dietary fat and serum cholesterol levels for 2 large groups, rural and industrial, in Delhi were presented and the incidence of atherosclerosis in these groups was assessed, purely from electrocardiographic evidence. In this paper, the results of a similar study undertaken in individuals of good social class (viz. professional men, business executives, a group of women medical students) and 2 urban low-socioeconomic groups are presented. The results of these 2 studies are compared.

## MATERIAL AND METHODS

### *High-Socioeconomic Group*

**Men.** The 100 individuals studied were men distributed among the various professions as follows: doctors 14, business executives 21, engineers 28, sportsmen (amateur hockey players) 15, and Sikhs 22. The last group was chosen for study as it was reputed to have a high-fat intake, although all the individuals did not belong to the same profession. They were all of high-socioeconomic status.

**Women.** Twenty-four women medical students of the Lady Hardinge Medical College were also studied.

### *Urban Low-Socioeconomic Groups*

Included in this group were 26 hospital coolies and 22 gardeners. The oral questionnaire method of taking complete diet histories, thorough physical examination including electrocardiography and fluoroscopy, biochemical investigations for serum total cholesterol level, urinalysis for albumin and sugar, and the criteria for diagnosing coronary

atherosclerosis were all employed as described in previous papers.<sup>1-3</sup>

There was no attempt at selection of population groups and all were random samples of apparently normal people. Only certain individuals from the rural and industrial low-income groups were willing to give blood because of fear of the needle prick and the "draining away of blood" and not for any other reasons.

## RESULTS

### *Incidence of Atherosclerosis*

On the sole basis of history of angina or of myocardial infarction there was not one case of ischemic heart disease in the low-income group but in the upper classes there were 2 such patients. On the basis of electrocardiograms there was a 4 per cent (4 out of 100) incidence of abnormal electrocardiograms in the high-income group and a 3 per cent (1 out of 34) in the rural group. The other low-income groups had no abnormality in the electrocardiograms. However, as the electrocardiograms were taken for all the men in the high-income groups and for only 34 out of 222 rural men, and for 28 out of 486 industrial workers studied, the figures were not strictly comparable. Also, of the 4 abnormal electrocardiograms in the high-income group, 2 were definite infarction patterns, one showed left bundle-branch block, and the other right bundle-branch block. In the low-income groups the one abnormality noted was left bundle-branch block.

In a large series that is being studied at present the number of abnormal electrocar-

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TABLE 1.—Data in the Various Social Groups

| Group                           | No. of cases | Average age, yrs. (range) | Average weight, lbs. (range) | Daily fat intake in Gm. (range) | Average cal. (%) from fats | Serum cholesterol levels mg. % (range) |                      | Electrocardiographic incidence of atherosclerosis (No. of EKGs done) |
|---------------------------------|--------------|---------------------------|------------------------------|---------------------------------|----------------------------|--|----------------------|--|
|                                 |              |                           |                              |                                 |                            | 40 years Below                         | 40 years Above       |  |
| High-socioeconomic groups (men) | 100          | 34.9 (20-65)              | 141.7 (102-208)              | 106.3 (46.7-187.9)              | 32.8                       | 220.4±57.3 (91-337)                    | 255.8±54.8 (94-408)  | 4% (100)   |
| Industrial workers (men)        | 197          | 32.2 (18-70)              | 121.7 (88-192)               | 80.9 (2-196)                    | 24.5                       | 168±33.7 (106-265)                     | 169±30.5 (112-270)   | Nil (28)   |
| Rural population (men)          | 133          | 38.0 (10-75)              | 105.8 (84-182)               | 67 (0-250)                      | 27.5                       | 181±37.5 (95-297)                      | 188±35.5 (106-297)   | 3% (34)  |
| Coolies (men)                   | 26           | 34.3 (16-60)              | 122.7 (95-178)               | 39.3 (0-95)                     | 17.6                       | 136.5±40.9 (81-222)                    | 200.8±44.3 (142-265) | 0 (26)   |
| Gardeners (men)                 | 22           | 36.9 (20-65)              | 105.4 (80-127)               | 25.6 (0-82)                     | 9.2                        | 159.2±17.6 (130-188)                   | 180.0±22.3 (148-225) | 0 (22)   |
| Rural population (women)        | 136          | 29.6 (11-60)              | 106.8 (80-176)               | 38.5 (0-124)                    | 25.1                       | 175±44.0 (72-305)                      | 183±38.5 (100-248)   | 0 (44)   |
| Medical students (women)        | 24           | 21.1 (19-23)              | 108.6 (90-140)               | 86.4 (30-122)                   | 40.6                       | 174.1±35.3 (130-261)                   | —                    | —  |

diagrams was only 8 of 334 (an incidence of 2.4 per cent) in the low-income groups, and 12 of 216 (5.5 per cent) in the high-income groups, which was nearly double the incidence in the former.

#### Dietary Fat Intake

The men of the high-socioeconomic group had a much higher fat intake, from 47 to 188 Gm. per day (table 1). The percentage of calories derived from fats ranged from 30.7 per cent among the business executives to 35.4 per cent among the engineers, with an average of 32.8 per cent. About two thirds of the ingested fat was from animal sources, being mainly butter, and the remaining one third consisted of vegetable oils, both hydrogenated and nonhydrogenated.

The high-fat intake among the women medical students was due to the lower total consumption of calories, mainly from carbohydrates.

Among the low-socioeconomic groups, the gardeners had the lowest fat intake followed by coolies, industrial workers, rural women, and rural men, in that order.

The range of fat intake was wide in all the groups, being greatest among the industrial workers and rural men.

#### Serum Total Cholesterol Levels

The difference in serum total cholesterol levels between the high- and low-socioeconomic groups was very striking, there being a difference of at least 39 mg. per cent between the rural men (who had the highest cholesterol levels among the poor classes) and the high-socioeconomic group below the age of 40 (table 1). Above age 40 the smallest difference was 55 mg. The coolies and gardeners, who had lower fat intakes than the rural or industrial group, had correspondingly lower serum cholesterol levels below age 40 but not above.

The various factors that might be responsible for this difference were considered in turn:

*Age (table 2, fig. 1).* Among the high-socioeconomic groups there was a definite increase in serum total cholesterol levels with age, this being most marked after the age of 40; there was a difference of 40 mg. per cent between the fourth and fifth decades. The slight fall after the fifth decade might be partly attributed to the small number of cases in this age group.

Figure 1 demonstrates the differences among the various groups in the cholesterol trends with age. In every age group the

TABLE 2.—Variation in Serum Total Cholesterol with Age

| Age in years   | Industrial workers (men) |  | Najafgarh rural population (men) |   | High-income group (men) |   |
|----------------|--------------------------|--|----------------------------------|---|-------------------------|---|
|                | No. of cases             | T.S.C.* in mg. % $\pm$ std. dev. (range) | No. of cases                     | T.S.C. in mg. % $\pm$ std. dev. (range) | No. of cases            | T.S.C. in mg. % $\pm$ std. dev. (range) |
| 10—19          | 6                        | 169 $\pm$ 30<br>(131-190)                | 23                               | 170 $\pm$ 40<br>( 95-252)               | 3                       | 190.7<br>(156-232)                      |
| 20—29          | 87                       | 164 $\pm$ 25<br>(120-220)                | 49                               | 186 $\pm$ 42<br>(104-293)               | 45                      | 222.1 $\pm$ 57.8<br>(122-337)           |
| 30—39          | 73                       | 174 $\pm$ 40<br>(106-265)                | 23                               | 176 $\pm$ 31<br>(129-297)               | 23                      | 220.7 $\pm$ 56.5<br>( 91-331)           |
| 40—49          | 20                       | 180 $\pm$ 40<br>(130-270)                | 21                               | 191 $\pm$ 21<br>(106-255)               | 17                      | 262.5 $\pm$ 65.3<br>( 94-408)           |
| 50—59          | 11                       | 150 $\pm$ 30<br>(112-155)                | 17                               | 185 $\pm$ 47<br>(115-297)               | 12                      | 245.2 $\pm$ 39.2<br>(173-326)           |
| Below 40 years | 166                      | 168<br>(106-265)                         | 95                               | 181<br>( 95-297)                        | 71                      | 220<br>( 91-337)                        |
| Above 40 years | 31                       | 169<br>(112-270)                         | 38                               | 188<br>(106-297)                        | 29                      | 256<br>( 94-408)                        |

TSC=total serum cholesterol.

high-socioeconomic group (men) had a considerably higher serum total cholesterol level.

The rise in the serum cholesterol levels with age was insignificant at any age among the rural men, probably significant ( $p = 0.05$ ) among the industrial workers from the fourth to the fifth decade,<sup>1</sup> but definitely significant ( $p = 0.01$ ) among the high-socioeconomic group from the fourth to the fifth decade. In the high-socioeconomic group the serum cholesterol levels between the average ages of 18 and 57 years showed a rise of 2.2 mg. per cent per year of age. Among the rural men and industrial workers between the same ages the rise per year of age was only 0.3 mg. per cent. The difference in the rise per year of age in the high- and low-socioeconomic groups was significant.

**Body Weight (table 3, fig. 2).** In another paper<sup>3</sup> it was demonstrated that for the same age and height the high-socioeconomic classes had higher body weights than the poor men. The influence of body weight on serum cholesterol levels in the different groups is shown in figure 2 and table 3.

In both groups there was a definite increase of serum total cholesterol levels with increase in body weight. However, for the same body

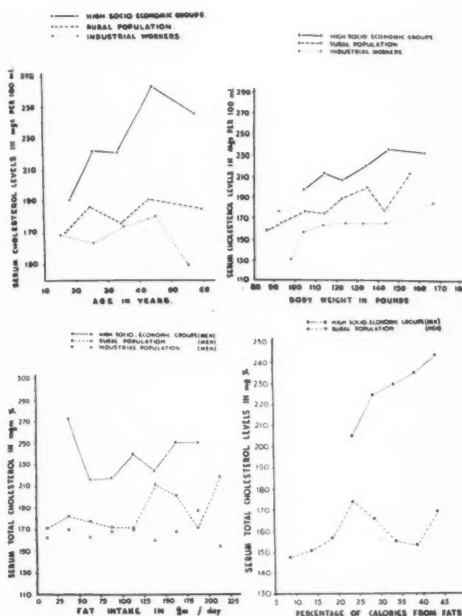


FIG. 1 Top left. Variations in serum cholesterol levels with age.

FIG. 2 Top right. Variations in serum cholesterol levels with body weight.

FIG. 3 Bottom left. Variations in serum cholesterol levels with daily fat intake.

FIG. 4 Bottom right. Variations in serum cholesterol levels with percentage of calories from fats.

TABLE 3.—*Variation in Serum Total Cholesterol with Body Weight (Men)*

| Range of body weight (pounds) | High-socioeconomic groups |                           |  | Industrial workers |                           |  | Rural population |                           |  |
|-------------------------------|---------------------------|---------------------------|--|--------------------|---------------------------|--|------------------|---------------------------|--|
|                               | No. of cases              | Mean body weight (pounds) | Mean serum total cholesterol level (mg. %) | No. of cases       | Mean body weight (pounds) | Mean serum total cholesterol level (mg. %) | No. of cases     | Mean body weight (pounds) | Mean serum total cholesterol level (mg. %) |
| 80—89                         | —                         | —                         | —  | —                  | —                         | —  | 3                | 86.6                      | 157.3                                      |
| 90—99                         | —                         | —                         | —  | 4                  | 98.0                      | 131.0                                      | 22               | 93.2                      | 164.7                                      |
| 100—109                       | 11                        | 104.1                     | 196.1                                      | 15                 | 104.0                     | 155.8                                      | 30               | 104.6                     | 175.6                                      |
| 110—119                       | 11                        | 113.7                     | 212.6                                      | 34                 | 113.3                     | 162.5                                      | 39               | 114.0                     | 173.0                                      |
| 120—129                       | 13                        | 122.9                     | 206.6                                      | 24                 | 124.3                     | 164.5                                      | 39               | 122.8                     | 188.0                                      |
| 130—139                       | 11                        | 133.5                     | 220.0                                      | 18                 | 132.5                     | 164.3                                      | 11               | 134.3                     | 199.6                                      |
| 140—149                       | 20                        | 144.5                     | 235.8                                      | 13                 | 143.3                     | 164.4                                      | 7                | 143.0                     | 176.4                                      |
| 150 & over                    | 30                        | 162.2                     | 232.8                                      | 10                 | 166.4                     | 182.9                                      | 6                | 155.3                     | 213.8                                      |

weight the high-socioeconomic group had a much higher serum total cholesterol level. The higher body weights, i.e., over 150 pounds were infrequent in the low-socioeconomic groups and there were comparatively fewer men with body weights over 130 pounds. In the high-socioeconomic group the lowest body weight recorded was not below 100 pounds, whereas among the rural men there were 25 individuals with body weights of less than 100 pounds.

**Fat Intake.** Figures 3 and 4, and table 4 show the variation in serum total cholesterol levels with fat intake, expressed as fat in grams and as percentage of calories from fats respectively, in the various groups. As already reported in our previous paper<sup>1</sup> the fat intake, when expressed in grams could not be correlated with the serum total cholesterol levels in the low-income groups. The same held good for the high-income groups in the present series. However, when fat intake was expressed as percentage of calories from fats the serum total cholesterol levels showed an upward trend in the case of the high-income groups and not in the poor classes. This discrepancy might be due to the percentage of calories from fats remaining almost the same at all ages in the high-income groups, whereas in the low-income groups the fat intake fell with age (table 5). This fall was due to the poor men being able to afford less food with advancing years instead of more as in the upper classes. The body weight also tended to fall with age in the poor classes and to rise

among the rich, probably due to the same reason.<sup>2</sup>

**Other Factors.** Among the other factors considered responsible for the higher serum cholesterol levels in the high-socioeconomic group were total calorie and protein intakes and physical activity. Total calorie and protein intakes were found to have no significant correlation with the total serum cholesterol levels. In the case of physical activity, however, the men of the high-socioeconomic groups were all sedentary (except one subgroup of amateur sportsmen playing hockey), whereas in the low-socioeconomic groups were men who indulged in "medium" activity.<sup>4</sup> When the sportsmen were compared to the other members of high-socioeconomic groups matched for age and weight, there were found to be only 3 individuals who could be so matched. The sportsmen had higher serum total cholesterol levels but their fat intakes were also higher. All these 6 men were aged 32 years or younger. The effect of physical activity could not be separately assessed in the present series.

Twenty-four engineers were matched for age and weight with 24 members of the rural and industrial groups. It was found that the average serum cholesterol levels were at least 40 mg. per cent higher among the engineers; the average values being 176.8 mg. per cent and 218.2 mg. per cent for the poor men and engineers respectively. The average age was 32.2 years and average weight 135 pounds in both groups.

TABLE 4.—*Variation in Serum Total Cholesterol with Daily Fat Intake*

| Fat intake<br>(Gm./day) | Industrial workers<br>(men) |  | Najafgarh rural<br>population (men) |  | High income<br>group (men) |  |
|-------------------------|-----------------------------|--|-------------------------------------|--|----------------------------|--|
|                         | No. of<br>cases             | Total<br>serum chol.<br>in mg. %<br>± std. dev.<br>(range) | No. of<br>cases                     | Total<br>serum chol.<br>in mg. %<br>± std. dev.<br>(range) | No. of<br>cases            | Total<br>serum chol.<br>in mg. %<br>± std. dev.<br>(range) |
| 0—24                    | 48                          | 162±38<br>(115-205)  | 33                                  | 171±40<br>(106-290)  | —                          | —  |
| 25—49                   | 45                          | 170±40<br>(106-260)  | 30                                  | 182±44<br>(95-297)   | 2                          | 273<br>(262-284)   |
| 50—74                   | 33                          | 163±40<br>(112-220)  | 24                                  | 178±35<br>(104-267)  | 15                         | 216.6±65.5<br>(103-177)                                    |
| 75—99                   | 26                          | 168±38<br>(120-265)  | 15                                  | 172±38<br>(130-293)  | 27                         | 220.3±52.2<br>(133-309)                                    |
| 100—124                 | 12                          | 170±41<br>(135-205)  | 5                                   | 171<br>(111-243)   | 20                         | 239.9±66.3<br>(142-337)                                    |
| 125—149                 | 12                          | 160±38<br>(120-210)  | 10                                  | 212±41<br>(159-289)  | 17                         | 224.8±54.2<br>(140-408)                                    |
| 150—174                 | 8                           | 168<br>(140-205)   | 4                                   | 202<br>(183-225)   | 8                          | 251.1±51.7<br>(184-331)                                    |
| 175—199                 | 6                           | 188<br>(150-225)   | 5                                   | 172<br>(148-196)   | 1                          | (251)  |
| 200—224                 | 4                           | 155<br>(125-250)   | 3                                   | 220<br>(207-240)   | —                          | —  |

## DISCUSSION

The conclusion that emerged from this study was that the serum total cholesterol levels were significantly higher in the high-income groups than in the low for the same age, body weight, and fat intake. There were, however, differences between the 2 groups in 2 respects. Firstly, with age there was a steady rise in the serum total cholesterol levels in the upper classes particularly after age 40, a feature absent in the low-income groups. Secondly, the effect of an increasing fat intake was also different when the latter was expressed as percentage of calories from fats: there being an upward trend in the case of the high-income groups and not in the low. Expressed as grams of fat this correlation was not present in either group. With regard to body weight there was an upward trend in the groups with increasing body weight but not more so in any social group.

The differences in rise of serum total cholesterol levels with age and fat intake could

probably be explained by gain in body weight and increasing fat intake with age among the well-to-do and not among the poor. The reason for the rise in the serum cholesterol levels with body weight is not clear. None of the men in this series could be considered obese. It has been demonstrated elsewhere that during periods of weight gain individuals have elevation of serum cholesterol levels.<sup>5</sup>

It is quite evident, however, that no single factor by itself, such as age, body weight, or fat intake was responsible for the differences in the serum total cholesterol levels between the 2 classes.

Our observations with regard to the differences in serum cholesterol in the high- and low-socioeconomic groups resemble those of Keys, in Spain<sup>6</sup> and in Italy,<sup>7</sup> among rich and poor classes and those of Bronte-Stewart et al. in South Africa,<sup>8</sup> and of Gopalan et al. among the rich and poor men in Coonoor,<sup>9</sup> who found a considerable difference in serum cholesterol levels between groups living on

TABLE 5.—*Variation in Fat Intake (Percentage of Calories) with Age*

| Range of age (years) | Najafgarh rural population |  | High-income groups |  |
|----------------------|----------------------------|--|--------------------|--|
|                      | No. of cases               | Mean percent-age of calories from fats | No. of cases       | Mean percent-age of calories from fats |
| 0—19                 | 26                         | 25.8                                   | 3                  | 34.2                                   |
| 20—29                | 41                         | 22.3                                   | 40                 | 33.7                                   |
| 30—39                | 27                         | 25.0                                   | 23                 | 33.3                                   |
| 40—49                | 23                         | 18.5                                   | 14                 | 29.8                                   |
| 50—59                | 18                         | 19.1                                   | 4                  | 31.1                                   |
| 60 and above         | 16                         | 18.4                                   | 5                  | 39.2                                   |

different dietary fat intakes. The age trend in the high-socioeconomic groups after 40 resembled that in Minnesotans<sup>10</sup> and rich Spaniards;<sup>6</sup> and in the low-socioeconomic groups, that found in poor Spaniards<sup>6</sup> and Italians.<sup>7</sup> The rise per year of age among Minnesotans and Indians of good social class was also similar, viz. about 2.2 mg. per cent per year. The poor Indians and the poor Neapolitans also showed a rise of only 0.3 mg. per cent per year of age.

The dietary fat intake among the high-socioeconomic groups in Delhi was almost the same as that for Cape Europeans,<sup>8</sup> and industrial workers in Slough.<sup>11</sup> It was much lower than the figures for Minnesota,<sup>10</sup> Boston,<sup>12</sup> Sweden,<sup>13</sup> and for professional men in Spain.<sup>6</sup>

It would appear, however, that the serum cholesterol levels of all populations deriving between 30 to 40 per cent of calories from fats were the same. Thus the Delhi figures among the high-socioeconomic groups resembled the figures for Minnesota, Boston, Madrid professional men, Slough industrial workers, Swedish firemen, and Cape Europeans although the first 3 had higher fat intakes.

#### SUMMARY

In a comparative study among low- and high-socioeconomic groups in Delhi the incidence of atherosclerosis as judged by electrocardiograms, the dietary fat intake, and the serum total cholesterol levels were found to be higher in the high-income groups.

In the high-income group the total serum cholesterol levels showed an upward trend with age and with increasing fat intake, both of these features being absent in the poorer classes. In both groups the serum cholesterol levels rose with increase in body weight.

The findings in the high-income groups with age were similar to the findings in Western countries among the well-to-do.

#### ACKNOWLEDGMENT

We are grateful to Mr. R. K. Lakhanpal, dietitian, Mr. Y. K. Bakshi, biochemist, and Miss Kalavathy, technician, for their help in the investigations.

#### SUMMARY IN INTERLINGUA

In un studio comparative de gruppos socio-economic basse e alte in Delhi, il esseva trovate que le indicationes electrocardiographic de atherosclerosis, le ingestion de grassia dietari, e le nivellos seral de cholesterol total esseva plus marcate in le gruppos de stato economic superior.

In le gruppos de stato economic superior, le nivellos seral de cholesterol total monstrava un tendentia de crescer con le etate del subjectos e con augmento del ingestion de grassia. Ambe iste factores esseva absente in le gruppos economicamente inferior. In ambe situationes le nivellos seral de cholesterol montava con le augmento del peso corporee.

Le constataciones in le gruppos de stato economic superior esseva simile al constataciones in gruppos prospere de paisas occidental.

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**Longmire, W. P., Jr., Cannon, J. A.: Direct-Vision Coronary Endarterectomy for Angina Pectoris.** *New England J. Med.* **259**:993 (Nov. 20), 1958.

Direct-vision coronary endarterectomy with resection of an almost totally occluding thickened intimal core from 1 or more of the main coronary vessels was performed in 5 patients with severe angina pectoris without myocardial infarction. In all cases blood flow was reestablished through the previously occluded vessel at the time of operation. One patient died of asystole developing near the completion of the operation. Of the 4 surviving patients 2 have been greatly improved. In all instances marked improvement has been noted in the electrocardiograms taken during exercise. The operation was devised on the premise that the patient with severe angina pectoris was likely to have an occlusive process near the aortic origin of at least 1 of the 3 major vessels and that the distal coronary tree beyond the occlusion was likely to be patent and supplied by blood through collateral anastomotic channels that had attained their maximum state of development. The results indicated that it was technically feasible to perform definitive endarterectomy in the major coronary arteries and to reestablish blood flow in such previously obstructed vessels.

SAGALL

# Differential Lung Function in Atrial Septal Defect

By H. A. FLEMING, M.D., M.R.C.P.

Studies of atrial septal defect have considered the total pulmonary blood flow and the contribution to the left-to-right shunt made by each lung. No studies have been reported of the separate flows through the 2 lungs. The present study in 25 cases was planned to investigate the differential pulmonary blood flow by bronchspirometry.

**C**LASSICAL studies of atrial defect<sup>1,2</sup> have mentioned only the total pulmonary blood flow and the appearance of pulmonary plethora on the chest radiograph. No mention has been made of differences between the two lungs.

The present study was suggested by investigations on the first patient in this series. He was a 50-year-old man whose atrial septal defect was confirmed by cardiac catheterization and subsequently repaired under hypothermia. The pulmonary vascular resistance was 4 units (table 1) and the pulmonary blood flow was small for an atrial septal defect. This atypical case presented several difficulties, among which was the difference in the radiographic appearance of vascularity of the 2 lungs (fig. 1). The right lung appeared plethoric and the left oligemic. Angiocardiography confirmed this impression, showing large, well-filled vessels in the right lung and attenuated vessels of normal distribution in the left. Bronchspirometry showed nearly normal distribution of the ventilation and vital capacity but 85 per cent of the oxygen uptake took place in the right lung and only 15 per cent in the left (normal 55 per cent on the right and 45 per cent on the left<sup>3</sup>). Bronchial abnormality was excluded by a normal left bronchogram.

Subsequently the posteroanterior radiographs of several patients with atrial septal defect appeared to show a similar, though less marked, discrepancy between the vascular markings in the 2 lungs. It was thought that there may be a regular difference in the

blood flows through the 2 lungs in atrial septal defect and the present study was planned to investigate this point.

When blood samples have been taken from the right and left pulmonary arteries, in cases of atrial septal defect, they have been of identical saturations. Samples from both right and left pulmonary veins have not been obtained frequently and data on their relative saturation are lacking. If it is presumed that they are identical, the blood flows through the individual lungs would be proportional to their oxygen uptakes, which can be measured by bronchspirometry. This presumption should be tested when opportunity offers for sampling from both right and left pulmonary veins in atrial septal defect.

## METHOD

The 25 patients were all adults in the hospital for cardiac catheterization or for repair of their atrial septal defect. The ages ranged from 15 to 51 years. Patients younger than 15 years were not investigated because of the difficulty of manufacturing a Carlens catheter small enough for them. In atrial septal defect the stature is frequently smaller than normal and the larynx is also often relatively small so that it was often necessary to use the smallest catheters made. Cases were otherwise unselected.

Two patients were clinically examples of the ostium primum type of defect in that they had a mitral pansystolic murmur and left axis deviation in the electrocardiogram.<sup>4</sup> Neither diagnosis has yet been confirmed by operation.

All cases but 1, which was so classically an ostium secundum type of defect that catheterization was not considered necessary, have been submitted to cardiac catheterization. This was frequently done within a few days of the bronchspirometry but was never simultaneous with it. The methods used have been described by Wood.<sup>5</sup> Seventeen patients have since had the defect repaired under

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TABLE 1.—Data in Twenty-five Cases of Atrial Septal Defect

| Patient            | Age | Sex       | Differential lung function % total by right lung |       |      | Cardiac catheterization |        |          | X-ray                   |        | Defect size (cm.) |
|--------------------|-----|-----------|--|-------|------|-------------------------|--------|----------|-------------------------|--------|-------------------|
|                    |     |           | O <sub>2</sub>                                   | Vent. | V.C. | P.B.F.                  | P.V.R. | P:S.B.F. | Lung plethors Ratio R:L | C.T.R. |                   |
| 1 A.D.             | 50  | M         | 85   | 53    | 50   | 5                       | 4      | 1.2      | 2.5                     | 53     | 2.5               |
| 2 E.K.             | 44  | F         | 55   | 25    | 43   | 4                       | 10     | 2        | 1.4                     | 54     | —                 |
| 3 W.T.             | 28  | F         | 63   | 59    | 61   | 35                      | <1     | 7        | 1.3                     | 71     | 4                 |
| 4 C.P.             | 15  | F         | 73   | 55    | 66   | 19                      | <1     | 2.5      | 2                       | 51     | 7x4               |
| 5 E.M.             | 33  | F         | 56   | 44    | 48   | 16                      | <1     | 3        | 3                       | 62     | 5                 |
| 6 N.H.             | 48  | F         | 77   | 32    | 48   | 16                      | <1     | 2.5      | 1                       | 50     | 4                 |
| 7 A.I.             | 47  | F         | 69   | 40    | 55   | 15                      | <1     | 5        | 1                       | 60     | 4x3               |
| 8 B.E.             | 23  | F         | 80   | 40    | 50   | 24                      | <1     | 4        | 2                       | 60     | 2.5               |
| 9 M.H.             | 40  | F         | 74   | 68    | 48   | 15                      | <1     | 4        | 1                       | 64     | 5                 |
| 10 A.C. (O.P.)     | 17  | F         | 82   | 46    | 50   | 23                      | 1      | 3.5      | 1                       | 59     | —                 |
| 11 K.L.            | 24  | M         | 65   | 65    | 28   | —                       | —      | —        | 1.3                     | 54     | —                 |
| 12 M.S.            | 29  | F         | 53   | 50    | 52   | 16                      | 1.3    | 3.5      | 1                       | 50     | 8x4               |
| 13 F.N.            | 51  | F         | 74   | 30    | —    | 18                      | <1     | 3        | 1.3                     | 50     | —                 |
| 14 H.W.            | 29  | F         | 70   | 50    | —    | 14                      | <1     | 4        | 1.7                     | 52     | 6x4               |
| 15 A.O.            | 49  | F         | 54   | 47    | —    | 13                      | 2      | 4        | 1.3                     | 60     | 5x3               |
| 16 J.S.            | 20  | M         | 67   | 60    | —    | 9                       | <1     | 1.5      | 1                       | 52     | —                 |
| 17 D.M.            | 35  | M         | 54   | 50    | —    | 13                      | <1     | 3        | 1                       | 68     | 6x5               |
| 18 S.C.            | 21  | F         | 65   | 34    | —    | 14                      | <1     | 2        | 1                       | 46     | —                 |
| 19 A.G.            | 18  | M         | 56   | 55    | 58   | 14                      | <1     | 2.5      | 1                       | 54     | —                 |
| 20 E.H.            | 19  | M         | 60   | 47    | 50   | 22                      | <1     | 3.2      | 1.3                     | 48     | 2.5               |
| 21 R.H.            | 45  | F         | 66   | 62    | 56   | 30                      | <1     | 8        | —                       | 68     | 4x6               |
| 22 R.H.            | 34  | M         | 61   | 51    | 50   | 28                      | <1     | 6        | 2.5                     | 43     | 3x4               |
| 23 L.P. (O.P.)     | 38  | F         | 70   | 60    | —    | 23                      | <1     | 5        | 1.5                     | 51     | —                 |
| 24 M.N.            | 23  | M         | 52   | 53    | 50   | 15                      | <1     | 3        | 1.3                     | 55     | 3                 |
| 25 J.H.            | 19  | F         | 58   | 68    | 55   | 15                      | <1     | 2.5      | 1                       | 46     | 1.5x2             |
| Average            | 32  | 8M<br>17F | 65.5   | 51.0  | 51.0 | 17.3                    | <1     | 3.7      | 1.43                    | 55.2   |                   |
| Standard deviation |     |           | 9.6  | 11.4  | 7.7  |                         |        |          |                         |        |                   |

O.P., Ostium primum type defect; O<sub>2</sub>, oxygen uptake; Vent., ventilation; V.C., vital capacity; P.B.F., pulmonary blood flow (L./min.); P.V.R., pulmonary vascular resistance (units); P:S.B.F., ratio of pulmonary to systemic blood flow; C.T.R., cardiothoracic ratio.

hypothermia by Sir Russell Brock, using the technic described by Ross.<sup>6</sup> The size of the defect (table 1) and the presence of anomalous pulmonary veins were assessed in these cases. All were examples of the ostium secundum type of defect, 3 being of the sinus venosus variety.<sup>7</sup> In the majority of the cases a bilateral thoracotomy permitted examination of both lungs, but latterly a right-sided approach has been used.

Bronchspirometry was carried out in the supine posture with the Carlens catheter and the technic described by Fleming and West.<sup>8</sup> As already reported,<sup>9</sup> this method has now been personally used in over 400 cases without ill effect and is a simple and harmless method of investigation.

## RESULTS

The chief findings are detailed in table 1. The studies of differential lung function are

reported as the percentage of the total function carried out by the right lung. In this series the oxygen uptake varied from 52 to 85 per cent, with an average of 65.5 per cent, that is, from normal to a very considerable increase. In contrast the ventilation and the vital capacity averaged slightly below the normal figure (fig. 2). There was no constant relationship between the oxygen uptake and the ventilation or the vital capacity. Figure 3 shows the traces recorded at bronchspirometry in a case near the average for the series.

The percentage oxygen uptake in the right lung has been plotted against age, size of defect, pulmonary blood flow, systemic blood flow, the ratio of the 2 blood flows, and the cardiothoracic ratio, without any relationships



FIG. 1. Posteroanterior roentgenogram (case 1) showing greater vascularity of the right lung and moderate enlargement of the heart.

emerging. It also appeared to be unrelated to the presence of symptoms or to the pulmonary vascular resistance.

#### *Radiologic Findings*

**Lung Fields.** The vascularity of each lung was independently assessed by 2 observers grading them 0 to 4 on the posteroanterior film. The ratio of the 2 was also estimated. It was soon apparent that this was a very difficult judgment to make, as cardiac enlargement commonly so encroached on the left lung field that little of it was visible for assessment. Fluoroscopy was not helpful. Angiocardiography in 2 cases confirmed the opinion that the increase in vascularity was greater on the right. Figure 4 illustrates an average case in which the peripheral vessels are more marked on the right than the left and in whom 61 per cent of the oxygen uptake occurred on the right side.

The radiologic assessment of the relative vascularity of the 2 lungs correlated poorly with the distribution of the oxygen uptake, but this is not surprising in view of the difficulties mentioned. It should be noted that the attempted radiologic assessment is on an anatomic and not a physiologic basis and need not be closely related to the relative flows in

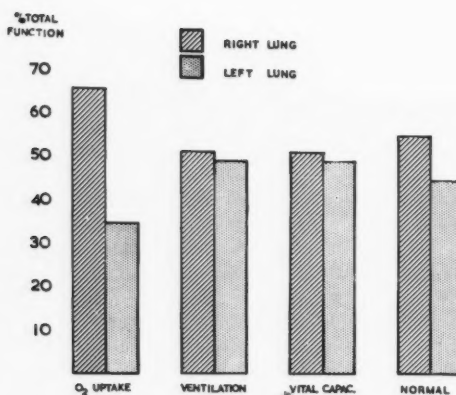


FIG. 2. Average results obtained at bronchospirometry in 25 cases of atrial septal defect. The standard deviations are 9.6 for the oxygen uptake, 11.4 for the ventilation, and 7.7 for the vital capacity.

the vessels. When the pulmonary vascular resistance is low, however, an approximate relationship would be anticipated between the appearance of vascularity and the actual flow in the lung.

Postoperatively the lungs appeared radiographically to be of equal and normal vascularity, this usually meaning a reduction in the size of the peripheral vessels on both sides but the right more than the left.

**Heart Size.** The heart size was estimated as a cardiothoracic ratio and an estimate was also made of the relative encroachment on the right and left lung fields. In moderate enlargement the increase was chiefly to the left of the spine, but in greater degrees the right atrium often extended more into the right lung. No precise estimate could be made but there were examples which suggested that particular enlargement to the left was sometimes associated with diminished function of the left lung.

#### *Operative Findings*

When bilateral thoracotomy was used, the bulk of the right lung was frequently observed to be greater than that of the left. An example of this is shown in figure 5. More marked cases occurred but a photographic record was not made. Similarly, in cases of

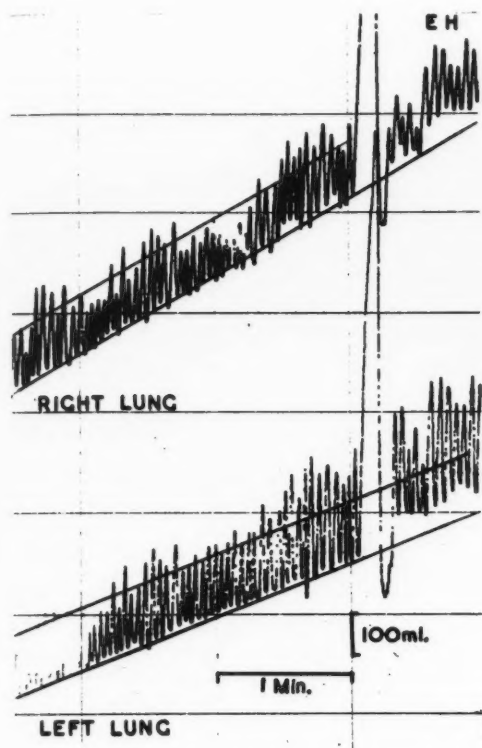


FIG. 3. Bronchspirometric traces from patient no. 20, a near average for this study. Sixty per cent of the oxygen uptake, 47 per cent of the ventilation, and 50 per cent of the vital capacity were carried out by the right lung.

anomalous venous drainage of the right upper lobe that lobe occupied a greater than normal volume though the lung was anatomically complete. In such cases the affected lobe or lung was more rigid and filled with more blood than the left lung. Some degree of this difference appears to be common in atrial septal defect but no attempt has been made to relate it to the measured relative pulmonary blood flow.

#### *Lung Fields in Other Cases with Central Arteriovenous Shunts*

The posteroanterior radiographs of 15 cases of patent ductus arteriosus and 10 cases of ventricular septal defect were examined. No differences could be seen in the vascular-



FIG. 4. Posteroanterior roentgenogram of case 22, a typical atrial septal defect. The disparity in the vascularity of the two lungs is obvious though less marked than in the atypical situation in figure 1. The moderate cardiac enlargement is chiefly to the left.

ity of the 2 lungs. No adult cases of patent ductus or ventricular septal defects have been available for differential lung function studies. It should be noted that Swan and others<sup>10</sup> using indicator-dilution techniques, reported that in patent ductus and ventricular septal defect each lung makes a similar contribution to the volume of the shunt. No cases of anomalous venous drainage of an entire lung have been seen. The findings in such cases, if the lungs were normal, would provide interesting evidence of the mechanism of the abnormal differential pulmonary blood flows in atrial septal defect. Reports suggest that anomalously draining lungs frequently also suffer bronchial dysgenesis;<sup>11-13</sup> functional results may, therefore be accepted only after full investigation of the bronchial anatomy. It has been stated<sup>14</sup> that the volume of blood shunted through anomalously draining lung is related to the number of lobes involved. However, the bronchial anatomy of these cases was not studied and this statement must be treated with reserve. Studies in patients with the sinus venosus type of atrial septal defect in which the defect was repaired, but



FIG. 5. Patient no. 20. The two lungs at bilateral thoracotomy seen from the patient's feet. The right lung is more bulky than the left.

the anomalously draining veins were not corrected, would also give interesting information.

#### DISCUSSION

In patients with atrial septal defect it has been established that the ventilation and the vital capacity of the right lung is slightly less than normal and that the oxygen uptake is greater. This increase in the proportion of the oxygen uptake carried out on the right side may be considerable. No completely satisfactory explanation has been reached.

The first factor that has been considered is the relationship of the right pulmonary veins to the atrial septal defect. In the ostium secundum type of defect the right pulmonary veins drain into the left atrium close to the septum and there may be little tissue separating them from the right atrium. If there is anomalous drainage of the right upper lobe, it goes to the right of the septum. These situations are well shown in the figures published by Lewis and others.<sup>15</sup> It has been demonstrated by dye-dilution techniques<sup>10, 16</sup> that an average of 84 per cent (75 to 97 per cent) of the blood from the right lung crosses the atrial septal defect while only 54 per cent (35 to 75 per cent) of the blood from the left lung does so. It seemed probable that this fact was related to the observations made in this study. It is known that the shunt in atrial septal defect depends on the difference in the filling resistance of the 2 ventricles and that

the right is the more distensible.<sup>2, 17</sup> It was therefore thought possible that with the large volumes of flow concerned, the slightly smaller resistance to outflow from the right lung could encourage the flow on that side, particularly as the vessels are commonly nearly maximally distended. Although in a large atrial septal defect there is no pressure gradient between the 2 atria, in cases in sinus rhythm, a gradient has been demonstrated with differential manometry, from left to right during ventricular systole.<sup>18</sup> This gradient again would assist the outflow from the right lung.

This explanation of the observations made in this study gains no support from the results obtained from the 2 cases of presumed ostium primum type of defect in which 70 and 82 per cent respectively of the pulmonary blood flow was taking place through the right lung. In this condition the defect is lower and more anterior, so that the right pulmonary veins are not in close relation to it and there may also be an additional shunt at ventricular level. Swan and others<sup>16</sup> have shown that in this type of defect the mixing of the venous blood from the 2 lungs is nearly complete and there is little preferential shunting of blood from the right lung. This has been commended<sup>19</sup> as a diagnostic point. In such cases, with the theory advanced, it would be expected that the blood flow, and therefore the oxygen uptake, would be normally distributed between the 2 lungs. The fact that this has not been so in these 2 cases is thought to weaken the thesis. In ostium primum defect, however, the situation of the interatrial communication and its hemodynamic effects vary widely, and until the detailed anatomy in these 2 cases is known, they by no means invalidate the theory. Further studies in proved cases of ostium primum are needed.

Studies in the relationship of the pulmonary vascular resistance to the pressure in the atrium into which the pulmonary veins are draining,<sup>20-22</sup> suggest that raising the atrial pressure lowers the resistance. The atrial pressures studied were all much greater than in the present series and the results are probably not applicable in these cases of

atrial septal defect in which the vessels are usually maximally dilated and tend to behave like a system of rigid tubes.

The second factor considered is the direction of the blood flow in the main pulmonary artery. It seems unlikely that the differential blood flow is related to this, as anatomically it would appear to favor the left rather than the right pulmonary artery. This point is reinforced by the frequency with which post-stenotic dilatation of the left pulmonary artery is seen in pulmonary valve stenosis.

Thirdly, the mechanical effect of the enlarged heart in the left chest was considered. The bulk of the cardiac enlargement is commonly into the left hemithorax so that in the posteroanterior radiograph, much of the left lower lobe is obscured. In this study there are several examples of patients with a large heart in the left chest in which the left lung carried an unusually small proportion of the total blood flow. There are also cases of considerable cardiac enlargement, however, with less disturbance of the flow relationship. At bilateral thoracotomy in the supine position, it is common to find the large heart compressing the left lung. If the volume of the heart were a significant factor it might be expected that the ventilation and the vital capacity in the left lung would be affected in similar proportion to the oxygen uptake, but there is a slight tendency in the opposite direction. It is possible that the pressure of the heart on the left lung forces an increased volume of blood into the right lung, thereby decreasing the distensibility of the lung tissue while increasing the oxygen uptake. That this may contain some truth is suggested by the observation at operation that the right lung feels more rigid. It would not explain the increase in volume and rigidity of an anomalously draining lobe.

The problem is presented in the hope that additional evidence may be produced to elucidate the mechanisms involved. Postmortem injection studies of the pulmonary vasculature would be of interest and it is planned to follow the effect of the repair of the defect on this distribution of blood flow.

#### SUMMARY

In atrial septal defect a greater than normal proportion of the blood flow is through the right lung. This flow may be considerable and can often be suspected from the postero-anterior radiograph and may be confirmed by bronchspirometry. At surgery the right lung or anomalously draining lobes are often found to be unduly voluminous and more rigid than the normally draining lung.

Various explanations for these findings are offered. The most attractive invokes the preferential draining of the blood from the right lung across the defect. A possible objection to this thesis arises in 2 cases of presumed ostium primum defect in which there was also an increased proportion of the flow through the right lung.

The enlargement of the heart into the left chest may also contribute to the situation. It is possible that both these factors are involved.

#### ACKNOWLEDGMENT

I am indebted to Dr. Paul Wood, Dr. R. V. Gibson, and Sir Russell Brock for permission to study patients under their care, to Dr. F. J. Prime for access to the Physiology Department, Institute of Diseases of the Chest, and Mr. B. P. Wheeler of the Physiology Department for technical assistance. The photographic work has been done by Mr. A. Curd of the Institute of Diseases of the Chest.

#### SUMMARY IN INTERLINGUA

In le presentia de defectos atrio-septal, un plus que normal proportion del fluxu de sanguine passa via le pulmon dextere. Iste fluxu es a vices considerabile. Frequentemente illo pote esser suspicite super le base de radiogrammas postero-anterior e confirmate per bronchspirometria. Al operation il es frequentemente constatate que le pulmon dextere o lobos a drainage anormal es plus voluminose e plus rigide que pulmones a drainage normal.

Es presentate varie explicationes de iste constataciones. Le plus attractive invoca le drainage preferential de sanguine ab le pulmon dextere a transverso le defecto atrio-septal. Un objection possibile contra iste theses es presenta con le constatacion que in 2 casos

de un supponite defecto del ostio prime il etiam habeva un augmentate proportion de fluxu vie le pulmon dextere.

Le allargamento del corde a in le thorace sinistre es forsan etiam un factor contributori. Il es possibile que ambe le mentionate factores es implicate in le situation.

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# Changes in Proteins and Lipoproteins in Diabetes and their Relationship to Vascular Degeneration

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The cause of atherosclerosis and reason for its high incidence in diabetes are not known. In this study proteins and lipoids of serums of patients with diabetes or atherosclerosis are examined by paper electrophoresis to determine whether such changes may be a common factor for both of these conditions.

THIS paper presents data on lipid and protein changes in the serum of various groups of subjects, with or without diabetes and with or without atherosclerotic lesions. Comparisons of these data might indicate the significance of the common metabolic alterations sometimes held responsible for the development of vascular degeneration.

## METHODS AND MATERIALS

The 97 subjects studied have been grouped in 7 classes (table 1): class 1, 30 normal subjects, 16 to 48 years old, without clinical signs of atherosclerosis; class 2, 27 older subjects (aged 36 to 93) with clinical signs of atherosclerosis; classes 3 to 7, 40 diabetic subjects, 10 being without clinical signs of vascular degeneration, the others presenting various vascular complications. The last class includes 5 cases with albuminuria, hypertension and retinopathy, suggesting the diagnosis of Kimmelstiel-Wilson glomerulosclerosis; 2 cases were verified at autopsy.

Protein electrophoresis was performed by the method of Dustin<sup>1</sup> on Whatman paper no. 1 strips, which were stained with bromophenol blue and read after elution of the chromogenic material.

Electrophoresis of the lipoproteins was effected with the same apparatus and paper, 0.15 ml. of serum being used per test; staining was carried out by the method of Jencks and Durrum<sup>2</sup> for 10 hours in 60 per cent alcohol saturated with red O. The strips were washed with tap water and read after elution with 20 per cent acetic alcohol. With this method electrophoresis for ½ hours at 300 volts yields well separated  $\alpha$ - and  $\beta$ -lipoprotein fractions. In order to esti-

mate absolute quantities of lipids transported by each of the 2 lipoprotein fractions, "total colorable lipids" have been measured by a technic derived from that of Swahn<sup>3</sup>: on equal square pieces of Whatman paper no. 1, increasing quantities were deposited (0.02 to 0.04 to 0.06 ml.) of serum and of a test solution of 1 per cent triolein in absolute alcohol. After stains were applied as described for lipoproteins, photometric reading of the eluate of each specimen yielded figures expressing the total amount of "colorable serum lipids" in milligrams per cent of triolein per 100 ml. serum. Values of  $\alpha$ - and  $\beta$ -lipoprotein fractions were then estimated in milligrams of triolein per 100 ml. serum. Sensitivity and reproducibility of these methods have been tested by repeating 10 times the assay on the same serum. The results indicate standard errors between 4.5 and 7.6 per cent for protein fractions (except  $\alpha$ -1 globulin), of 4.3 per cent for colorable serum lipids, of 6 per cent for  $\alpha$ - and of 2.4 per cent for  $\beta$ -lipoproteins.

Cholesterol has been measured by the method of Schoenheimer and Sperry,<sup>4</sup> and total lipids by the method of Bloor.<sup>5</sup>

## RESULTS

Comparison of the 2 series of nondiabetic subjects showed significant alterations in serum proteins and lipids in the group of older atherosclerotic patients. The changes in proteins were characterized by a decrease in the albumin fraction and an increase in the globulins, specially in the  $\alpha$ 2, but also the  $\beta$ - and  $\gamma$ -globulins. The alteration in lipids consists in an increase of cholesterol, of total lipids, of colorable lipids, and more specifically of the  $\beta$ -lipoproteins.

The findings in 2 series of younger or elder diabetic subjects without signs of im-

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TABLE 1.—Results of Serum Protein Fractions, Cholesterol, Lipids, and Lipoproteins

| Classes   | Age Limits | No. of cases | Serum protein fractions (% of total) |                     |                      |                      | Serum lipids (mg. for 100 ml.) |             | Serum lipoproteins |                        |             |                      |
|---|------------|--------------|--------------------------------------|---------------------|----------------------|----------------------|--------------------------------|-------------|--------------------|------------------------|-------------|----------------------|
|   |            |              | Alb                                  | $\alpha_1$          | $\alpha_2$           | $\beta$              | $\gamma$                       | Tot. chol.  | Tot. lip. (Blood)  | % Tot. amount $\alpha$ | $\beta$     |                      |
| 1. Normal subjects†                                     | 18-48      | 30           | 67.4±4.2                             | 4.3±0.8             | 7.0±1.3              | 8.3±1                | 13.1±2.6                       | 150±210*    | 629±136†           | 23.9±6.6               | 132±31      | 430±94               |
| 2. Atherosclerosis difference from 1                    | 36-93      | 27           | 59.9±5.4<br>$p<0.001$                | 4.9±0.9<br>$p<0.01$ | 9.0±2.4<br>$p<0.001$ | 10.4±1.7<br>$p<0.01$ | 15.9±4.0<br>$p<0.01$           | 246±74<br>— | 913±193<br>—       | 19.5±7.2<br>$p<0.02$   | 139±40<br>0 | 601±183<br>$p<0.001$ |
| 3. Diabetes without complication difference from 1      | 15-55      | 10           | 64.7±5.1                             | 4.6±0.6             | 6.6±1.2              | 9.4±1.5              | 14.8±2.4                       | 255±66      | 997±80             | 22.6±7.1               | 164±37      | 609±210              |
|   |            |              | 0                                    | 0                   | 0                    | $p<0.02$             | 0                              | —           | —                  | 0                      | $p<0.02$    | $p<0.01$             |
|   |            |              | $p<0.02$                             | 0                   | $p<0.02$             | 0                    | 0                              | 0           | 0                  | 0                      | 0           | 0                    |
| 4. Diabetes with mild atherosclerosis difference from 1 | 55-79      | 10           | 64.7±5.0                             | 4.1±0.8             | 7.1±1.0              | 10.1±1.0             | 14.0±3.5                       | 239±40      | 983±259            | 20.3±6.9               | 139±36      | 605±222              |
|   |            |              | 0                                    | 0                   | 0                    | $p<0.001$            | 0                              | —           | —                  | 0                      | 0           | $p<0.01$             |
|   |            |              | $p<0.02$                             | $p<0.02$            | $p<0.05$             | 0                    | 0                              | 0           | 0                  | 0                      | 0           | 0                    |
|   |            |              | 0                                    | 0                   | 0                    | 0                    | 0                              | 0           | 0                  | 0                      | 0           | 0                    |
| 5. Diabetes with severe arteritis difference from 1     | 50-80      | 6            | 59.5±5.8                             | 4.7±0.6             | 9.7±1.9              | 11.0±2.2             | 15.1±3.1                       | 326±74      | 1100±161           | 19.8±6.0               | 160±32      | 692±197              |
|   |            |              | $p<0.001$                            | $p<0.001$           | $p<0.001$            | $p<0.001$            | 0                              | —           | —                  | 0                      | 0           | $p<0.001$            |
|   |            |              | 0                                    | 0                   | 0                    | 0                    | 0                              | $p<0.05$    | 0                  | 0                      | 0           | 0                    |
|   |            |              | 0                                    | 0                   | $p<0.01$             | 0                    | 0                              | 0           | 0                  | 0                      | 0           | 0                    |
|   |            |              | 0                                    | 0                   | $p<0.01$             | 0                    | 0                              | $p<0.02$    | 0                  | 0                      | 0           | 0                    |
| 6. Diabetic retinopathy difference from 1               | 45-70      | 9            | 60.7±6.6                             | 4.2±0.8             | 8.4±1.9              | 11.1±3.3             | 15.5±2.1                       | 227±70      | 794±138            | 16.3±4.9               | 130±36      | 679±123              |
|   |            |              | $p<0.001$                            | 0                   | $p<0.02$             | $p<0.001$            | $p<0.02$                       | —           | —                  | $p<0.01$               | 0           | $p<0.001$            |
|   |            |              | 0                                    | 0                   | 0                    | 0                    | 0                              | 0           | 0                  | 0                      | 0           | 0                    |
|   |            |              | 0                                    | 0                   | 0                    | 0                    | 0                              | 0           | 0                  | 0                      | 0           | 0                    |
| 7. Kimmelstiel-Wilson difference from 1                 | 42-62      | 5            | 48.9±6.2                             | 5.6±1.8             | 12.0±3.5             | 12.8±2.3             | 20.7±7.3                       | 283±43      | 1012±337           | 13.4±4.4               | 110±25      | 764±207              |
|   |            |              | $p<0.001$                            | $p<0.01$            | $p<0.001$            | $p<0.001$            | $p<0.001$                      | —           | —                  | $p<0.01$               | 0           | $p<0.001$            |
|   |            |              | $p<0.001$                            | 0                   | $p<0.05$             | $p<0.02$             | 0                              | 0           | 0                  | $p<0.05$               | $p<0.02$    | 0                    |
|   |            |              | $p<0.001$                            | 0                   | $p<0.001$            | $p<0.01$             | $p<0.05$                       | 0           | 0                  | 0                      | 0           | 0                    |
|   |            |              | $p<0.001$                            | $p<0.05$            | $p<0.001$            | $p<0.01$             | $p<0.05$                       | 0           | 0                  | 0                      | 0           | 0                    |
|   |            |              | $p<0.02$                             | 0                   | 0                    | 0                    | 0                              | 0           | 0                  | 0                      | 0           | 0                    |
|   |            |              | $p<0.01$                             | 0                   | $p<0.05$             | 0                    | 0                              | 0           | 0                  | 0                      | 0           | 0                    |

\*Normal values after Thannhauser.<sup>20</sup>†Normal values after Adlersberg et al.<sup>21</sup>

‡For each group mean values and standard errors ( $\sigma$ ) are given. Student-Fischer test has been applied to compare the different groups. Significance is indicated by the  $p$  values; nonsignificant results by zero. A dash means that no calculation has been performed, owing to insufficient data.

important atherosclerotic lesions are not significantly different from each other. Compared to nondiabetic controls, these 2 groups of diabetic subjects show the following changes: increase in  $\beta$ -globulins, increase in cholesterol and total lipids, and increase in colorable lipids, due to marked elevation of the  $\beta$ -lipoproteins.

The fifth group of 6 diabetic patients with severe peripheral atherosclerosis displays the same changes in serum proteins as the group of atherosclerotic patients without diabetes: decrease in albumin, increase in globulins, specially  $\alpha$ 2- and  $\beta$ -globulins. In this group the values of cholesterol, of lipids and of  $\beta$ -lipoproteins are very high.

In the group with diabetic retinopathy the same changes in proteins and in the lipids except cholesterol were observed. Changes are most marked both for proteins and lipids in the class of diabetic patients with retinopathy and nephropathy. The albumin fraction is very depressed and the increase in globulins concerns all fractions. Cholesterol and total lipids reach extremely high values and the marked increase in colorable lipids is due to the very high augmentation of the  $\beta$ -lipoproteins.

Although the diabetic condition is characterized by a definite increase in total serum lipids, in most cases the respective fractions transported with  $\alpha$ - and  $\beta$ -proteins are not markedly altered. However the partition of the lipids between  $\alpha$  and  $\beta$  fractions is profoundly altered in cases with clinical evidence of specific abnormalities of the vessels, and most so in patients with diabetic glomerulosclerosis.

#### DISCUSSION

The methods used for paper electrophoresis of serum proteins are satisfactory for clinical research. The results obtained in this investigation are closely comparable to those reported by Jencks et al.<sup>6</sup> It is true that paper electrophoresis used in the determination of lipoproteins yield only semiquantitative results. As discussed by Eder,<sup>7</sup> however this method has definite advantages over more intricate procedures.

With these limitations it appears that the changes in serum proteins and lipids, which are observed in diabetes and in atherosclerosis, are very similar.

In the present study, atherosclerosis is characterized by a reduction in serum albumin and an increase in  $\alpha$ 2-,  $\beta$ - and  $\gamma$ -globulins and by a definite increase of the serum cholesterol, total lipids and  $\beta$ -lipoproteins. These observations are in keeping with numerous previous reports on proteins,<sup>6,8,9</sup> on cholesterol,<sup>10,11</sup> on lipids, and on electrophoretically separated lipoproteins.<sup>7,13-16</sup>

Diabetes, even when under good control and without vascular degeneration, differs from the normal state by a definite increase of  $\beta$ -globulins and the same alterations in lipid metabolism, that are found in non diabetic atherosclerosis. With development of vascular lesions, the anomalies do not undergo qualitative changes but  $\alpha$ 2-globulins increase as in atherosclerosis; also the cholesterol and other lipids may reach very high values.

Similar observations have been made by other authors for proteins,<sup>17-20</sup> cholesterol and lipids,<sup>21-27</sup> lipoproteins separated by ultracentrifugal techniques,<sup>23,27,28</sup> and by paper electrophoretic methods.<sup>3,15,29</sup>

While some of these changes, in particular the increase of  $\alpha$ 2-globulins, only become apparent with the development of severe atherosclerotic changes, it is difficult to establish to what extent the metabolic changes are primary or secondary to the vascular lesions. Schertenleib and Tuller,<sup>31</sup> in a recent paper report "a tendency for those protein changes to be present *before* there is clinical evidence of vascular damage." It is clear that in the Kimmelstiel-Wilson syndrome many of the changes may be due to some functional alteration similar to those of the nephrotic syndrome. However, the observations made in uncomplicated diabetes suggest that increase in the  $\beta$ -lipoproteins and in the total lipids together with elevation of the  $\beta$ -globulins play a definite role in the development of the vascular degeneration, so common in the course of diabetes.

## SUMMARY

Paper electrophoresis of serum proteins and lipids has been performed in 97 subjects viz. 30 normal subjects, 27 nondiabetic patients with atherosclerosis, 40 diabetic patients, some with vascular degeneration.

Certain alterations in serum proteins and lipids are of constant occurrence in atherosclerosis: decrease in albumin, increase in  $\alpha_2$ -,  $\beta$ - and  $\gamma$ -globulins, increase in serum cholesterol, total lipids and  $\beta$ -lipoproteins. Some of these changes, especially increased  $\beta$ -globulins and lipids, are present in diabetes even without detectable signs of vascular degeneration.

## SUMMARIO IN INTERLINGUA

Electrophorese a papiro esseva effectuate pro le proteinas e lipidos seral de 97 subjectos, i.e. 30 normales, 27 atheroscleroticos non diabetic, e 40 diabeticos, certes sin e alteres con degeneration vascular.

Certe alterationes del proteins e lipidos seral occurre constantmente in atherosclerosis. Illos es: Reductione de albumina, augmento del globulinas  $\alpha_2$ ,  $\beta$ , e  $\gamma$ , e augmento del cholesterol seral, del lipidos total, e del lipoproteinas  $\beta$ . Certes de iste alterationes, specialmente le augmento del globulinas  $\beta$  e del lipidos, es presente in diabete mesmo in le absentia de detegibile signos de degeneration vascular.

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Subsequently, in the celebrated Commentaries upon which our grandfathers in the profession were educated, Heberden gave a fuller account of his experience with the disease. The name which he adopted can not be regarded as altogether satisfactory, since it was already in use in designating affections of the throat, with which its literal meaning—a strangling—is much more in harmony. In one sense, however, the term is fairly appropriate, since, as noted by Gairdner, the words anxiety and anguish, expressive of two of the most prominent features of the disease, have a derivation from the same Greek word as angina.—WILLIAM OSLER. *Lectures on Angina Pectoris and Allied States*, 1897.

# Left Ventricular Activation Time in Normal Men

By TAKASHI WADA, M.D.

Simultaneous recordings from right and left precordial leads in 50 normal individuals were obtained. The duration of rS in lead  $V_1$  was always equal to or greater than the duration of qR in lead  $V_7$ . Evidence is presented to support the thesis that the duration of rS in lead  $V_1$  is a more accurate index of left ventricular activation time than the duration of qR in the left precordial leads.

**I**N DIRECT LEADS obtained through a small electrode attached to the epicardium, there is a nearly perpendicular return of the R wave from its peak to the base line. This intrinsic deflection marks the extinction of the electric potential of the small core of ventricle to which the electrode is applied. In precordial leads, where a relatively large electrode is at a considerable distance from the heart, there is a more gradually sloping downstroke, or intrinsicoid deflection, since electric activity does not disappear simultaneously in all parts of the wide area subtended by the electrode.

In clinical electrocardiography, the time from the onset of the initial deflection to the peak of the R wave in precordial leads over the left ventricle is widely used for timing and measuring left ventricular activation. An electrode placed at  $V_5$  or  $V_6$  registers an R wave because of the predominating positive potentials derived from the anterior and lateral wall of the left ventricle. Negative potentials derived from the activation of the posterior wall of the left ventricle influence the duration of the positive phase in these leads and cause slurring or notching on the descending limb of the R wave. Thus these leads reflect counteracting positive and negative potentials. A reversed situation occurs at  $V_8$

where the positive deflection created by the activation of the posterior wall is altered by the negativity of the anterior wall. Therefore clinical left precordial electrocardiograms do not reflect precisely the entire left ventricular activation.

It may be assumed, then, that unless the descending limb of the R wave in the left precordial leads is nearly perpendicular, activation of some portion of the left ventricle is still continuing after the R wave has reached its peak. Measurements made on these leads then would not represent the true activation time of the entire left ventricle.

On the other hand, negative potentials over the right precordium (S wave) are believed to be reciprocals of the positive potentials created by the activation of the entire left ventricle.<sup>1</sup> Therefore it is believed that this reflected negativity might be a more accurate measurement of complete left ventricular activation.

The purpose of this study was to examine the precordial leads in a large group of normal individuals, and to determine which lead most accurately measured the total activation time of the left ventricular wall.

## MATERIALS AND METHODS

Fifty men with normal cardiovascular systems, as judged by a careful history and examination, were selected for study. The group consisted of 14 resident physicians, 19 medical students, 7 hospital employees, and 10 convalescent noncardiac patients. Their ages ranged from 22 to 39 years with a mean of 29 years.

Precordial electrocardiograms,  $V_{3R}$  through  $V_8$  were taken on each subject in the recumbent position with a Sanborn Twin-Beam Cardiette. An initial recording consisted of lead  $V_8$  on 1 channel

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This investigation was supported by grant H-1492, National Heart Institute, National Institutes of Health, U.S. Public Health Service, The Michigan Heart Association, The R. C. Mahon Foundation and the C. Cox Foundation.

taken simultaneously with each lead from  $V_{3R}$  through  $V_7$  on the other channel. Lead  $V_8$  was later changed to  $V_7$  as the constant, since there was no difference in the duration of the R wave in  $V_8$  and  $V_7$ . However, the magnitude of the complex was usually greater in  $V_7$  than in  $V_8$ , thus facilitating measurements. The second run consisted of  $V_1$  as the constant reference lead taken simultaneously with  $V_{3R}$  through  $V_7$ . Standardization was the customary 1 mv. per 10 mm. Paper speed was 75 mm. per second, so that the space between each vertical line of photographic paper was 3 mm. in width and 0.04 second in duration. With use of 3 $\times$  magnifying lens the duration of the various components of the QRS complex was estimated to 0.005 second. The final figure represented an average of 3 independent measurements on 3 separate occasions. A total of 450 individual readings was made; 330 of these showed identical results in 3 separate determinations. The maximum difference in repeated measurements of the same tracing was 0.01 second. Measurements were made primarily in leads  $V_1$  and  $V_7$  because of their opposite locations in relation to the heart.

#### RESULTS

##### *Configuration and Timing of Initial Deflection in $V_1$ and $V_7$*

In all tracings the initial deflection in  $V_1$  was upright. In 46, the initial deflection in  $V_7$  was a q wave and began simultaneously with the r in  $V_1$ . In the remaining 4, the q wave was not present in  $V_7$  and the R wave began later than the initial deflection in  $V_1$ . The delay was long enough to allow for a q wave if electromotive forces had been strong enough to produce one (fig. 1).

Of the 46 tracings with a measurable q in  $V_7$ , the r wave in  $V_1$  was notched or slurred in 27 instances. This notch or slur, which represents the peak of the initial r in  $V_1$ , coincided in time with the nadir of the q wave in  $V_7$  (fig. 2). Nineteen of the 46 tracings presented a smooth r in  $V_1$ . In 3 of these the nadir of  $qV_7$  occurred simultaneously with the peak of  $rV_1$  (figs. 3 and 4). In the remaining 16 tracings the nadir of  $qV_7$  occurred earlier than the peak of  $rV_1$ , presumably coinciding in time with the forces that were insufficient to cause a notch or slur in  $V_1$  (fig. 5).

Thus it is seen that in all instances manifesting a q wave in  $V_7$ , the duration of this

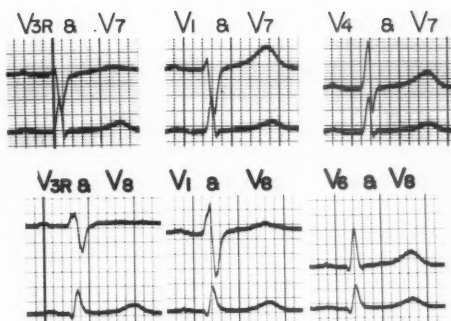


FIG. 1 Top. Simultaneous tracings of  $V_1$  and  $V_7$  reveal a delay in the inscription of the initial deflection in  $V_7$ . The nadir of S in  $V_1$  occurred later than the peak of the R in  $V_7$ , but did not coincide with the nadir of the s wave in  $V_7$ . (Patient 14)

FIG. 2 Bottom. Simultaneous onset of the initial deflection in  $V_1$  and  $V_8$ . A notched r in  $V_{3R}$  and a slurred r in  $V_1$  coincides with the nadir of the q wave in  $V_8$ . A marked difference in the duration is seen from the onset of r to the nadir of S in  $V_1$  (0.055 second) and from the onset of q to the peak of R in  $V_8$  (0.045 second). (Patient 7)

deflection was equal to or less than the duration of the r wave in lead  $V_1$ .

##### *Time Relationship of the Nadir of $SV_1$ and Peak of $RV_7$*

In 12 of the 50 tracings studied, the nadir of  $SV_1$  coincided with the peak of  $RV_7$  (fig. 3). In 15, the nadir of  $SV_1$  fell at various points on the descending limb of the R wave in  $V_7$  or immediately after its return to the isoelectric line (figs. 1, 2, 4, and 5). In 28, a small s wave was present in  $V_7$ , the nadir of which coincided in time with the nadir of  $SV_1$  in 16 instances. In the remaining 12 tracings the nadir of  $SV_1$  fell at various points on the descending limb of  $RV_7$ . It should be emphasized that the nadir of the S wave in  $V_1$  never occurred earlier than the peak of the R wave in  $V_7$  or in any other lead over the left ventricle.

##### *Duration of QRS Complex in Leads $V_1$ and $V_7$*

Details of this analysis are presented in table 1. There was a significant difference in duration between rS, measured from the onset of the r to the nadir of the S wave, in lead  $V_1$  and qR, measured from the onset of the

q to the peak of the R wave in lead  $V_7$ . The duration of the former ranged from 0.035 to 0.055 second with a mean of 0.048 second. The duration of the latter ranged from 0.030 to 0.050 second, with a mean of 0.042, thus indicating that a greater potential was re-

flected by the negativity in lead  $V_1$  than the positivity in lead  $V_7$ . In 6 instances, rS in  $V_1$  was as much as 0.015 second greater than qR in  $V_7$  (table 1, cases 5, 15, 21, 33, 39, and 44).

In no instance was the duration of rS in lead  $V_1$  shorter than the duration of qR in lead  $V_7$ .

#### DISCUSSION

It has been accepted generally that in normal individuals the activation of the septum occurs from both directions. However, the left side of the septum is activated from 0.01 to 0.015 second earlier than the right.<sup>2</sup> This vectorial force produces a small r in the right ventricular leads that occurs simultaneously with a small q in the left ventricular leads. This was demonstrated in 46 tracings of the 50 subjects studied in this series.

In 27 instances in which the r in lead  $V_1$  was notched, the notch coincided with the nadir of the q wave in lead  $V_7$  and presumably was derived from the same force, that of the septal activation. As the nadir of the q wave in  $V_7$  is passed, the activation of the free wall of the left ventricle has progressed sufficiently to replace the downstroke of the q wave.

The negativity recorded as S in  $V_1$  is due to the reciprocal transmission of positive potentials derived from the forces created by activation of the left ventricular wall.<sup>1</sup> In 12 of the 50 tracings studied here, the nadir of the S wave in  $V_1$  coincided with the peak of the R wave in  $V_7$ . In the remaining 36, there was no coincidence; the nadir of  $SV_1$  always occurred after the peak of  $RV_7$ . This lack of coincidence and longer duration of rS in lead  $V_1$  were noted by Rapaport and his associates<sup>3</sup> although no actual measurements were made. It has been noted also that in general the magnitude of QRS complex in lead  $V_1$  is greater than that in  $V_7$ .

It appears that the larger amplitude of the QRS complex in lead  $V_1$  and its longer duration provide a more accurate reflection of the entire left ventricular activation time than the potential registered by lead  $V_7$ . Because of

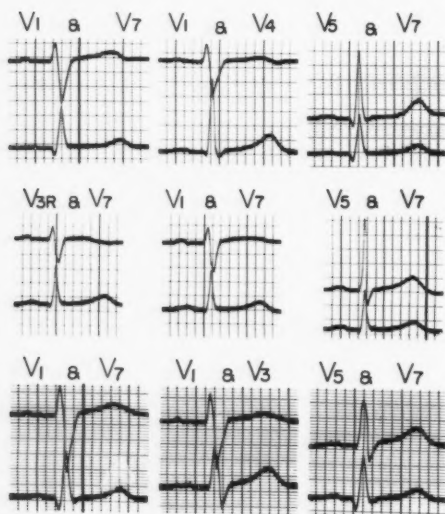


Fig. 3 *Top*. Simultaneous onset of the initial deflection in  $V_1$  and  $V_7$ . The peak of a smooth r in  $V_1$  coincides with the nadir of q in  $V_7$  indicating a common source of forces, clearly the septal activation. The duration is identical from the onset of the r to the nadir of the S and from the onset of q to the peak of R in  $V_7$ . (Patient 2)

Fig. 4 *Middle*. Simultaneous onset of the initial deflection in  $V_1$  and  $V_7$ . However, the initial deflection in  $V_7$ , a q wave, is very small and its nadir occurred earlier than the peak of the r wave in  $V_1$ . The duration from the onset of the q to the peak of R in  $V_7$  is shorter than the duration from the onset of the r to the nadir of S in  $V_1$ . This suggests that some activation of the left ventricle is still going on after the inscription of the peak of  $RV_7$ . (Patient 12)

Fig. 5 *Bottom*. Simultaneous onset of the initial deflection in  $V_1$  and  $V_7$ . The tall, smooth r wave in  $V_1$  and its peak coincides with the nadir of the q wave in  $V_7$ . The duration from the onset of the r to the nadir of the S in  $V_1$  is slightly longer than the duration from the onset of q to the peak of R in  $V_7$ . Note a delay in the inscription of the initial deflection in  $V_3$ , the transitional area. If this were not present, the longer duration of RS in  $V_3$  might be a better index for the total activation time of the ventricles. (Patient 31)

TABLE 1.—Duration of QRS Complex in Leads  $V_1$  and  $V_7$ 

| Case no. | Duration of rS in $V_1$ | Duration of qR in $V_7$ | Case no. | Duration of rS in $V_1$ | Duration of qR in $V_7$ |
|----------|-------------------------|-------------------------|----------|-------------------------|-------------------------|
| 1        | 0.045                   | 0.045                   | 26       | 0.045                   | 0.035                   |
| 2        | 0.050                   | 0.050                   | 27       | 0.055                   | 0.045                   |
| 3        | 0.045                   | 0.040                   | 28       | 0.045                   | 0.045                   |
| 4        | 0.050                   | 0.045                   | 29       | 0.045                   | 0.040                   |
| 5        | 0.055                   | 0.040                   | 30       | 0.050                   | 0.045                   |
| 6        | 0.055                   | 0.050                   | 31       | 0.050                   | 0.045                   |
| 7        | 0.055                   | 0.045                   | 32       | 0.055                   | 0.045                   |
| 8        | 0.045                   | 0.045                   | 33       | 0.055                   | 0.040                   |
| 9        | 0.040                   | 0.040                   | 34       | 0.040                   | 0.035                   |
| 10       | 0.040                   |                         | 35       | 0.045                   | 0.035                   |
| 11       | 0.045                   | 0.040                   | 36       | 0.045                   | 0.040                   |
| 12       | 0.050                   | 0.040                   | 37       | 0.050                   | 0.040                   |
| 13       | 0.040                   | 0.040                   | 38       | 0.045                   | 0.040                   |
| 14       | 0.045                   |                         | 39       | 0.050                   | 0.035                   |
| 15       | 0.050                   | 0.035                   | 40       | 0.045                   | 0.040                   |
| 16       | 0.050                   | 0.045                   | 41       | 0.050                   | 0.040                   |
| 17       | 0.040                   | 0.040                   | 42       | 0.040                   | 0.040                   |
| 18       | 0.050                   | 0.045                   | 43       | 0.045                   | 0.045                   |
| 19       | 0.050                   | 0.050                   | 44       | 0.050                   | 0.035                   |
| 20       | 0.055                   |                         | 45       | 0.045                   | 0.045                   |
| 21       | 0.055                   | 0.040                   | 46       | 0.050                   | 0.045                   |
| 22       | 0.050                   | 0.040                   | 47       | 0.045                   |                         |
| 23       | 0.050                   | 0.040                   | 48       | 0.045                   | 0.040                   |
| 24       | 0.050                   | 0.040                   | 49       | 0.050                   | 0.045                   |
| 25       | 0.035                   | 0.035                   | 50       | 0.045                   | 0.045                   |

An average measurement of 3 separate readings is shown above. There were 4 instances in which the q wave was absent in  $V_7$ , which accounts for the blank spaces in the table.

its position in relation to the left ventricular muscle mass, lead  $V_1$  reflects the over-all negativity during the activation of the free wall of this chamber. On the other hand, the location of the electrode at  $V_7$  is such that it cannot record the potentials of all portions of the left ventricle. The fact that the electrode at  $V_1$  is closer to the heart and that there is less interposition of lung between this electrode and the heart than there is between the heart and the electrode at  $V_7$  seems to account for the greater amplitude of the QRS complex in lead  $V_1$ .

Twenty-eight of the tracings in this study presented a qRs type of complex in lead  $V_7$ , in which the s wave reflected the activation of some portion of the heart other than the anterolateral wall beneath the electrode. In 16 of these, the nadir of the S wave in

TABLE 2.—Duration of Components of QRS Complex in  $V_1$ ,  $V_7$ , and Transition Zone

|  | Range (sec.)   | Mean (sec.) | Standard deviation (sec.) |
|--|----------------|-------------|---------------------------|
| Duration of r in $V_1$<br>(from the onset of<br>r to its peak)                                       | 0.015 to 0.030 | 0.020       | 0.00455                   |
| Duration of rS in $V_1$<br>(from the onset of r<br>to the nadir of the<br>S wave)                    | 0.035 to 0.055 | 0.048       | 0.006                     |
| Duration of qR in $V_7$<br>(from the onset of q<br>to the peak of<br>R wave)                         | 0.035 to 0.050 | 0.041       | 0.007                     |
| Duration of RS at the<br>transitional area<br>(from the onset of R<br>to the nadir of the<br>S wave) | 0.045 to 0.065 | 0.054       | 0.006                     |
| Duration of the widest<br>QRS complex  | 0.060 to 0.095 | 0.079       | 0.010                     |

$V_1$  coincided with the nadir of the s wave in  $V_7$ . This suggests a common source, presumably from forces arising from the activation of the posterior wall of the left ventricle. In the other 12 instances with a small s wave in lead  $V_7$ , the nadir of the  $SV_1$  fell at any point from the peak of the R wave in  $V_7$  to its isoelectric line. Activation of the crista supraventricularis causes this late negativity in the left precordial leads and at the same time relative positivity in the right precordial leads, but is manifested as the ascending limb of the S wave in lead  $V_1$ .<sup>4</sup>

The quantitative measurements of the QRS complexes described above are shown in table 2. The most pertinent measurements are those of the duration of rS, from the onset of the r to the nadir of the S wave in lead  $V_1$ , and the duration of qR, from the onset of the q to the peak of the R wave in lead  $V_7$ . The  $p$  value of the differences was less than 0.001. It is concluded, therefore, that lead  $V_1$  may be used routinely for more accurate determination of the left ventricular activation time in normal men than the usual leads over the left precordium. The reliability of the peak of the R wave in left ventricular

leads as an intrinsic or intrinsicoid deflection has also been questioned by others.<sup>5, 6</sup>

Wilson suggested that the true intrinsic deflection would be the lowest or most negative point and not the peak of the R wave.<sup>5</sup> Sodi-Pallares believed that the true intrinsic deflection occurs somewhere on the lower one half of the descending limb of the R wave. The results of the present study seem to indicate that the nadir of the S in  $V_1$  appears to approximate most closely the instant of arrival of the activation potential at the left ventricular epicardial surface. Thus an accurate measurement of the left ventricular activation time is provided.

#### SUMMARY AND CONCLUSIONS

Simultaneous electrocardiographic recordings using right and left precordial leads were taken in 50 normal individuals.

Detailed analyses of QRS complexes were made with special reference to leads  $V_1$  and  $V_7$ .

The duration of rS in lead  $V_1$ , from the onset of the r to the nadir of the S wave was always the same or greater than the duration of qR in lead  $V_7$ , from the onset of the q to the peak of the R wave.

The advantage of choosing lead  $V_1$  for the measurement of left ventricular activation time was discussed.

It is concluded that the duration of rS in lead  $V_1$  appears to be a more accurate index for the measurement of left ventricular activation time than the generally used measurement of left precordial complexes.

#### ACKNOWLEDGMENT

The author wishes to express his gratitude to Drs. Gordon B. Myers and Harper K. Helms, Detroit, Mich., and to Dr. James Baer, Dearborn, Mich., for their valued advice and cooperation in the performance of this study. The author is also grateful to Dr. John Ord for the statistical analyses and to Dr. Kouichi Tanaka for his assistance in writing the manuscript.

#### SUMMARY IN INTERLINGUA

Electrocardiogrammas simultanee a derivation dextero- e sinistro-precordial esseva obtenite ab 50 individuos normal.

Detaliate analyses de complexos QRS esseva effectuate con referentia special al derivationes  $V_1$  e  $V_7$ .

Le duration de rS in derivation  $V_1$  (i.e. le intervallo ab le declaration del unda r usque al nadir del unda S) esseva semper al minus equal al duration de qR in derivation  $V_7$  (i.e. al intervallo ab le declaration del unda q usque al zenit del unda R).

Es discutite le advantage de seliger le derivation  $V_1$  pro le mesuration del tempore de activation sinistro-ventricular.

Es concludite que le duration de rS in le derivation  $V_1$  es apparentemente un plus accurate indice pro le mesura del tempore de activation sinistro-ventricular que le usualmente emplateate parametros in le complexos precordial.

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## Left Ventricular Activation Time in Left Ventricular Hypertrophy and in Left Bundle-Branch Block

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Simultaneous tracings of right and left ventricular leads were taken in 6 dogs with experimentally produced left bundle-branch block, and in 30 clinical cases of left ventricular hypertrophy. In the experimental study it was found that the initial phase of the QRS complex in the right epicardial lead did not change its configuration or its duration after the production of left bundle-branch block. This observation offers a new concept of the septal and left ventricular activation in left bundle-branch block. It was concluded that a considerable portion of the left ventricle is activated normally in some cases of left bundle-branch block.

**A** METHOD of measurement of left ventricular activation time in normal subjects was discussed in a previous paper.<sup>1</sup> From a simultaneous recording of right and left precordial leads, it was found that the negativity recorded as an S wave in lead  $V_1$  was a reciprocal transmission of the positive potentials created by the activation of the left ventricular wall. Furthermore, it was concluded that the time interval from the onset of the initial deflection to the nadir of the S wave in  $V_1$  represents a better index of the left ventricular activation time than does the usually measured interval from the onset of the initial deflection (q wave) to the peak of the R wave in  $V_7$ .

While there is a marked change in the configuration of the initial phase of the left precordial complexes in clinical cases of left bundle-branch block, the initial phase of the right precordial complexes remains essentially unchanged.<sup>2, 3</sup> Although the configuration of the latter is similar to that found in normal subjects, the mechanism of its production is thought to be different. In normal hearts, according to a well known concept,<sup>3, 4</sup> the sep-

tal activation from left to right causes the inscription of an r wave in both right ventricular cavity and right ventricular leads.\* Upon activation of the right ventricular wall, further extension of the r wave occurs in the right ventricular leads. On the other hand, in left bundle-branch block, the initial activation of the septum from right to left causes a negativity in the right ventricular cavity. Nevertheless, despite this negativity, the right ventricular leads usually reveal r waves as seen in normal tracings. This discrepancy has been attributed to the early activation of the apical portion of the right ventricle.<sup>3, 4</sup> Following the initial positive deflection in right ventricular leads an S wave is inscribed both in normal tracings and in left bundle-branch block. This S wave is caused by activation of the free wall of the left ventricle in normal hearts and is attributed to the abnormally slow activation of the septum from right to left in cases of left bundle-branch block. The activation of the free wall of the left ventricle in left bundle-branch block would be expected to produce further negativity and deepening of the S wave in the right ventricular leads. However, according to the generally accepted concept,<sup>4</sup> activation of the left ventricular wall is manifested by the ascending limb of the S wave. But no adequate explanation is given for this.

\*The term "ventricular leads" will be used throughout this paper to include both epicardial and precordial leads.

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This investigation was supported by grant H-1492, National Heart Institute, National Institutes of Health, U.S. Public Health Service, the Michigan Heart Association, the R. C. Mahon Foundation and the C. Cox Foundation.

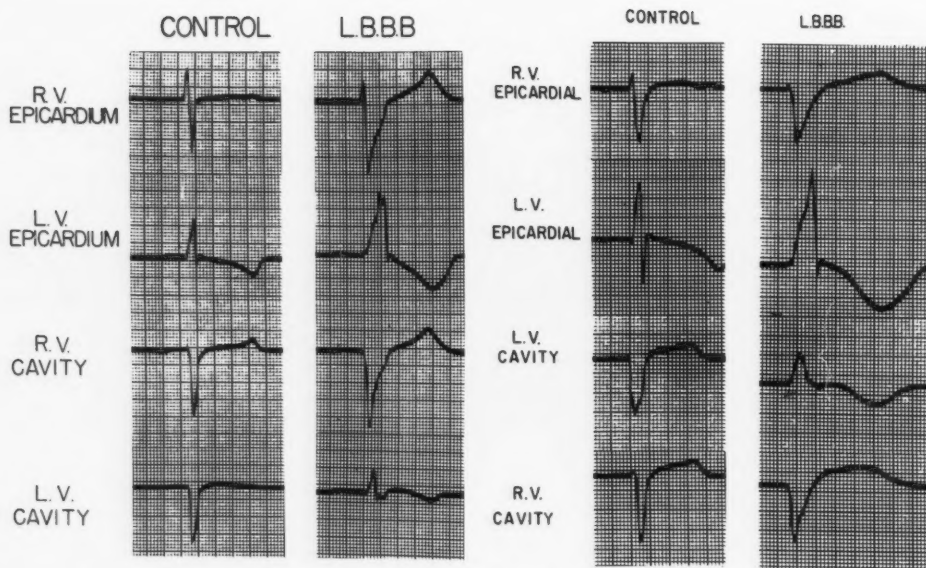


FIG. 1 *Left*. Intracavity and epicardial leads of dog no. 1. In control tracings the onset of the initial deflection of all 4 leads is simultaneous. The left intraventricular cavity lead shows some delay in the onset of the initial deflection after the production of left bundle-branch block. The right epicardial lead shows an rS pattern before and after left bundle-branch block. The time interval from the onset of the initial deflection to the nadir of the S wave is identical in both control and left bundle-branch block.

FIG. 2 *Right*. Intracavity and epicardial leads of dog no. 3. In control tracings, the onset of the initial deflection in all 4 leads is simultaneous. After the production of left bundle-branch block, the onset of the left intraventricular cavity lead is delayed. There is a marked change in left epicardial lead from qRs to Rs after left bundle-branch block, but the right epicardial lead remains essentially unchanged.

Experimental and clinical studies were undertaken to reconsider the mechanism of septal and left ventricular activation in left bundle-branch block. An attempt was also made to analyze the rS complex in right epicardial leads in dogs with experimental left bundle-branch block and in precordial leads in human patients with left ventricular hypertrophy with and without left bundle-branch block.

#### EXPERIMENTAL STUDY

##### *Materials and Methods*

Six dogs each weighing from 15 to 20 Kg. were used. The animals were anesthetized with sodium pentobarbital (25 to 35 mg. per Kg. of body weight). Maximum exposure of the heart was accomplished by a transverse sternal-splitting incision. Respiration was maintained with a constant flow of 100 per cent oxygen by means of a posi-

tive pressure apparatus. The pericardial fat was removed atraumatically. A small window was made in the pericardium overlying each atrium, and a small cotton-tipped intracavity electrode was inserted transatrially into each ventricular cavity. Another small cotton-tipped electrode was used to explore the entire surface of the heart through the intact pericardium in order to find complexes similar to  $V_1$  and  $V_7$  in human tracings. The rS type of complex typical of  $V_1$  could be found on the right ventricle near the septum and a qRs or Rs type of complex similar to  $V_7$  was obtained from the anterolateral wall of the left ventricle. The positions of the epicardial electrodes were similar to those of  $V_1$  and  $V_7$  in human tracings. Small saline-soaked cotton electrodes were gently sewn onto the epicardium through a small window in the pericardium. A control electrocardiogram was taken simultaneously from the 4 electrodes in the proper locations with a paper speed of 100 mm. per second, with a Sanborn 4-channel direct-writer. For more accurate meas-

urement of the rS duration in right epicardial leads, a Sanborn Twin-Beam Cardiette was used with a paper speed of 75 mm. per second. Left bundle-branch block was produced by inserting an iridectomy knife through the posterior portion of the left ventricle near the atrioventricular groove and severing the left bundle. The diagnosis of left bundle-branch block was based on the finding of an initial positive deflection in the left intraventricular cavity lead in the presence of a sinus rhythm.

#### RESULTS

In all instances, the control tracings revealed the simultaneous onset of the initial deflections in all 4 leads (figs. 1 and 2).

**Right Epicardial Complex.** In the control tracings, the right epicardial complex was of the rS type in all instances (fig. 3). Its average duration from the onset of the r to the nadir of the S wave was 0.021 second. After the production of left bundle-branch block, the rS complexes persisted, and the interval from the onset of r to the nadir of S was unchanged. The only marked change in the right epicardial complex after the production of left bundle-branch block was slurring and widening of the ascending limb of the S wave, which accounts for the increased duration of the entire QRS complex. The average QRS duration was 0.046 second in control tracings and 0.090 second after production of left bundle-branch block.

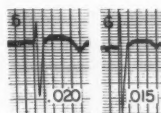
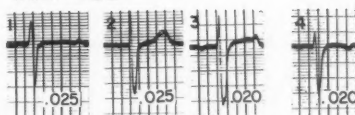
**Left Epicardial Complex.** In the 6 animals, 4 had an Rs type of complex in the control tracings (fig. 1). In the other 2 animals, the complexes were of the QRS type (fig. 2). After left bundle-branch block, however, all the complexes were of the Rs type with slurring of the R wave.

**Right Intraventricular Cavity Complex.** All but 1 showed an rS type of complex in the control tracings, the exception being a QS complex. After the production of left bundle-branch block, all the complexes were of the QS type.

**Left Intraventricular Cavity Complex.** All animals showed a QS type of complex in the control tracings. These became RS in type after production of left bundle block (figs. 1 and 2). In 4 instances there was consider-

#### DIRECT R.V. EPICARDIAL LEADS

##### CONTROL



##### L.B.B.B.

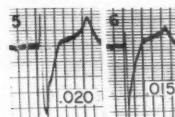
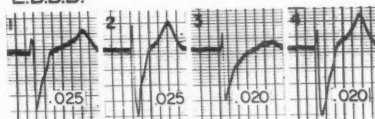


FIG. 3. Right epicardial leads in 6 dogs before and after the production of left bundle-branch block. The time from onset of r to nadir of S is indicated.

able delay in the inscription of the initial deflection (fig. 1).

**The Relationship of the Nadir of the S Wave in Right Epicardial and the Peak of the R Wave in Left Epicardial Leads.** In the control tracings, the nadir of the S wave in the right epicardial leads always occurred simultaneously with or later than the peak of the R wave in left epicardial leads. This relationship changed after the production of left bundle-branch block, when the nadir of the S wave in right epicardial leads always occurred earlier than the peak of the R wave in left epicardial leads.

#### CLINICAL STUDY

##### Materials and Methods

Thirty hypertensive patients with roentgenographic evidence of left ventricular enlargement were selected for this study. The duration of hypertension ranged from 4 to 15 years and the blood pressure varied from 160/110 to 240/140 mm. Hg, with a mean of 190/115 mm. Hg. All patients had a history of one or more episodes of congestive failure and were receiving digitalis

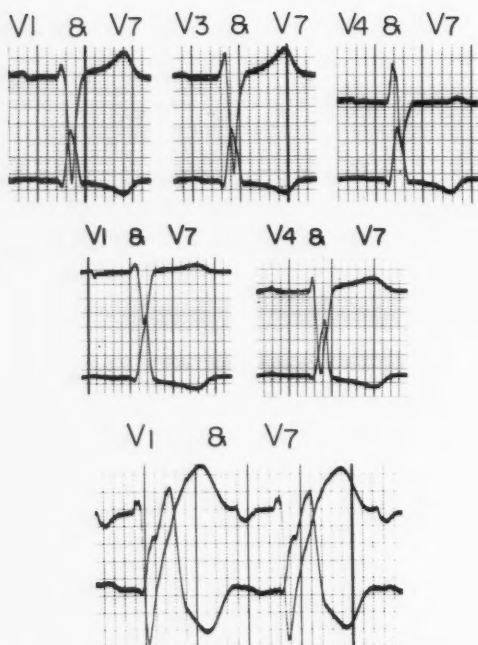


FIG. 4 *Top*. Standard 13 leads with simultaneous right and left precordial leads of patient no. 3, showing a typical pattern of left ventricular hypertrophy. There is a normal relationship of the nadir of the S wave in  $V_1$  and the peak of the R wave in  $V_7$ . The duration from the onset of the initial deflection in  $V_1$  to the nadir of the S wave is 0.065 second, indicating pure left ventricular hypertrophy.

FIG. 5 *Middle*. Simultaneous right and left precordial leads of patient no. 7. There is a distinct q wave in the left precordial leads. The duration from the onset of the initial deflection in  $V_1$  to the nadir of the S wave is 0.065 second, indicating left ventricular hypertrophy. Reversed relationship of S wave nadir in  $V_1$  and R wave peak in  $V_7$  suggests left bundle-branch block.

FIG. 6 *Bottom*. Simultaneous right and left precordial leads of patient no. 26. The entire QRS duration is 0.185 second in lead  $V_7$ . The simultaneous tracings of  $V_1$  and  $V_7$  disclose qrS and rrsR pattern. The ascending limb of the S wave in the right precordial leads is markedly slurred. The duration from the onset of the initial deflection in  $V_1$  to the nadir of the S wave is 0.07 second, indicating left ventricular hypertrophy. In addition, the reversed relationship of the nadir of the S wave in  $V_1$  and the peak of the R wave in  $V_7$  suggests left bundle-branch block. At autopsy the heart weighed 650 Gm., with left ventricular hypertrophy. There were some old infarctions and many new infarctions at left of septum. Multiple septal infarctions account for the left bundle-branch block.

preparations at the time of study. Patients with evidence of old myocardial infarction were included, but those with acute myocardial infarction were eliminated from this series. Patients with possible right ventricular enlargement were also excluded. The age of the patients ranged from 28 to 65 years with a mean of 52 years.

In all patients simultaneous recordings were made of lead  $V_1$  and of lead  $V_7$ , with each lead from  $V_{3R}$  to  $V_7$ , as described in the previous paper.<sup>1</sup> For reasons previously discussed<sup>1</sup> most of the measurements pertinent to this study were those of the complexes of lead  $V_1$  and  $V_7$ .

## RESULTS

*Onset and Configuration of the Initial Deflections.* Of the 30 tracings studied, 25 showed the onset of the initial deflection to be simultaneous in both  $V_1$  and  $V_7$  (figs. 4, 5, and 6). In the remaining 5 cases, there was a delay in the onset of the initial deflection in  $V_7$  in comparison to that of  $V_1$  (fig. 7). In no instance did the onset of the initial deflection occur later in  $V_1$  than in  $V_7$ . This indicates that lead  $V_1$  is a more accurate index than  $V_7$  for determining the onset of the initial deflection.

In  $V_1$  the initial deflection was positive in 23 cases (table 1). In the left precordial leads, including  $V_5$ ,  $V_6$ , and  $V_7$ , the initial deflection was positive in 9 instances.

*Time Relationship and Duration of Complexes.* In 23 of the 30 cases, the nadir of S in  $V_1$  occurred earlier than peak of R in  $V_7$  (figs. 6, 7, and 8). This finding was the reverse of that in normal cases. In these 23 instances, the relationship of S in  $V_1$  and R in  $V_7$  was exactly the same as that in experimentally produced left bundle-branch block in dogs. In 4 of the remaining 7 cases, the nadir of S in  $V_1$  occurred later than the peak of R in  $V_7$  (figs. 4 and 5), and in the last 3 instances the nadir of  $SV_1$  and the peak of  $RV_7$  were simultaneous.

The time intervals from the onset of the initial deflection to the nadir of the S wave in  $V_1$  varied from 0.045 to 0.080 second, with a mean of 0.057 second. The same interval in normal individuals ranged from 0.035 to 0.055 second, with a mean of 0.048 second. In 25 tracings the time interval from the onset of the initial deflection to the peak of

TABLE 1.—*Electrocardiographic Observations in Thirty Cases of Left Ventricular Hypertrophy\**

| Case no. | Type of QRS in V <sub>1</sub> | Type of QRS in V <sub>7</sub> | Duration from onset of initial deflection to nadir of SV <sub>1</sub> | Duration from onset of initial deflection to peak of RV <sub>7</sub> |
|----------|-------------------------------|-------------------------------|---|--|
| 1        | rS                            | qR                            | 0.065   | 0.055  |
| 2        | rS                            | qRs                           | 0.055   | 0.055  |
| 3        | rS                            | qR                            | 0.065   | 0.060  |
| 4        | rS                            | rsR                           | 0.065   | 0.070  |
| 5        | rS                            | qR                            | 0.055   | 0.080  |
| 6        | rS                            | qR                            | 0.065   | 0.080  |
| 7        | rS                            | qR                            | 0.060   | 0.080  |
| 8        | rS                            | R                             | 0.060   |  |
| 9        | rS                            | qR                            | 0.050   | 0.080  |
| 10       | rS                            | qR                            | 0.065   | 0.065  |
| 11       | rS                            | qR                            | 0.050   | 0.060  |
| 12       | rS                            | qR                            | 0.050   | 0.065  |
| 13       | rS                            | qR                            | 0.055   | 0.060  |
| 14       | rS                            | qR                            | 0.055   | 0.055  |
| 15       | rS                            | qR                            | 0.045   | 0.055  |
| 16       | rS                            | qR                            | 0.060   | 0.060  |
| 17       | rS                            | R                             | 0.045   |  |
| 18       | rS                            | R                             | 0.050   |  |
| 19       | rS                            | qR                            | 0.045   | 0.055  |
| 20       | rS                            | qRs                           | 0.065   | 0.060  |
| 21       | rS                            | qR                            | 0.060   | 0.065  |
| 22       | rsrS                          | qR                            | 0.065   | 0.075  |
| 23       | qrS                           | qrsR                          | 0.060   | 0.080  |
| 24       | qrS                           | qRs                           | 0.060   |  |
| 25       | qrS                           | qR                            | 0.055   | 0.070  |
| 26       | qrS                           | rsrsR                         | 0.070   | 0.14   |
| 27       | qrS                           | R                             | 0.080   | 0.090  |
| 28       | qrS                           | rsR                           | 0.055   | 0.075  |
| 29       | qrS                           | R                             | 0.055   |  |
| 30       | QS                            | R                             | 0.045   | 0.055  |

\*In 5 instances there was a delay in the inscription of the initial deflection in lead V<sub>7</sub>, which accounts for the blank spaces in the last column.

the R wave in V<sub>7</sub> was from 0.055 to 0.14 second, with a mean of 0.070 second. In 5 instances there was a delay in the inscription of the initial deflection in V<sub>7</sub> and these were not included in this analysis, since no definite moment of onset could be determined. This mean duration of 0.070 second is markedly different from the normal mean of 0.042 second. It is also evident that the duration of qR or R in V<sub>7</sub> exceeds the duration of rS, qrS, or QS in V<sub>1</sub> in this series, which was

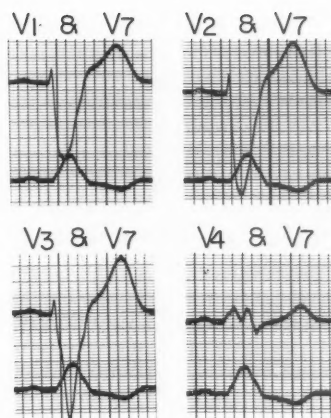


FIG. 7. Simultaneous right and left precordial leads of patient no. 8. The onset of the initial deflection in V<sub>7</sub> is delayed. The duration from the onset of the initial deflection in V<sub>1</sub> to the nadir of the S wave is 0.060 second. This indicates left ventricular hypertrophy. The reversed relationship of the nadir of the S wave in V<sub>1</sub> and the peak of the R wave in V<sub>7</sub> suggests left bundle-branch block. The late positivity is seen at the transitional area.

exactly opposite from what was found in normal subjects.

The entire width of the QRS complex varied from 0.10 to 0.185 second, with a mean of 0.12 second. The same value in normal individuals ranged from 0.095 second, with a mean of 0.079 second.

#### DISCUSSION

In both experimental and clinical left bundle-branch block, the definitive diagnosis is believed to rest upon the findings of an initial positive deflection in the left intraventricular cavity. However, even with this method there are often differences in the configuration and onset of the positive deflection. As seen in the present experimental study, there is sometimes a considerable delay in the inscription of this initial positive deflection when it is compared to other simultaneous leads. The R wave in the left intraventricular cavity lead is preceded by an isoelectric period in these instances (figs. 1 and 2). What this isoelectric period represents is unknown. It may be that 2 equal potentials arising from opposite sides of the septum activate the septum in transverse fashion, and thus

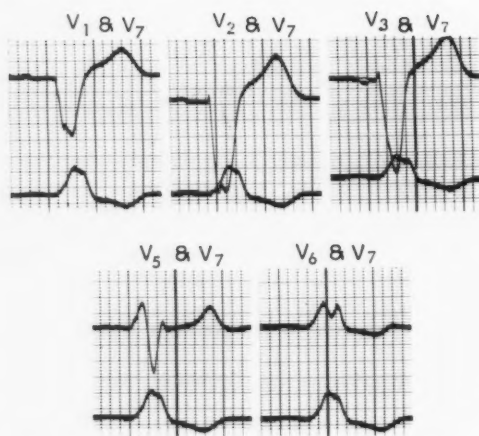


Fig. 8. Simultaneous right and left precordial leads of patient no. 27. There is a qRS pattern in leads  $V_1$  and  $V_2$ . The duration from the onset of the q to the nadir of the S wave in lead  $V_1$  is 0.08 second, indicating left ventricular hypertrophy. The duration of the R wave is 0.09 second. This suggests left bundle-branch block. Late positivity is seen at the transitional area.

neutralize each other. Another possible cause of the isoelectric period might be that potentials arising in the septum are not strong enough to register. Finally, the vector of these potentials may be at such an angle to the electrode in the left ventricular cavity that no deflection can be recorded.

Using a cathode-ray oscillographic method, Kenamer and his associates<sup>6</sup> found a similar discrepancy between the onset of the initial deflection in the left epicardial leads and that of left ventricular cavity potentials in experimental left bundle-branch block. These workers suggested an abnormally rapid transmission of the impulse to the epicardial surface of the left ventricle via an unknown pathway in cases of left bundle-branch block. In any event, it is suggested that the arrival of the impulse at the epicardial surface of the homolateral ventricle is not delayed when bundle-branch block is produced in dogs. The anatomic structure of the left bundle<sup>7</sup> is such that a certain type of left bundle-branch block may involve only a portion of the left bundle. According to Sodi-Pallares and his associates,<sup>8</sup>

the delay in the activation of the septum in some cases of left bundle-branch block can be limited to a very small portion of the septum. This small diseased portion of the septum could produce a prolonged septal activation up to 0.08 second. However, the remaining portion of the septum is not affected by the block and is activated normally. This observation is supported by the findings of a qRS type of complex in the left ventricular cavity in experimental left bundle-branch block.<sup>9</sup> In such an instance the greater potentials produced by the activation of the portion of the septum which is normally depolarized from left to right overwhelm the lesser potentials of this abnormally depolarized portion of the septum. This produces an initial negativity in the left ventricular cavity. Wener and others<sup>10</sup> demonstrated initial negativity in the left ventricular cavity in human cases of left bundle-branch block by means of esophageal leads. Smith and his associates<sup>11</sup> found both normal and delayed arrival of the impulse at the epicardial surface of the homolateral ventricle after the experimental production of "segmental bundle-branch block" in dogs.

These observations seem to cast doubt upon the classic concept<sup>12</sup> that in left bundle-branch block, left ventricular depolarization does not start until completion of the septal depolarization from right to left. In addition, they suggest that clinical bundle-branch block is partial or incomplete in nature.

In a preceding paper,<sup>1</sup> the nature and significance of the rS complex in right precordial leads were analyzed. It was concluded that this complex, measured from the onset of the initial deflection to the nadir of the S wave in  $V_1$ , represents an accurate measurement of the left ventricular activation time in normal subjects. This conclusion also appears to be true of epicardial tracings taken from the right ventricles of normal dogs. Although there is a distinct difference between epicardial and precordial leads, the same intervals from the onset of the initial deflection to the nadir of the S wave in right epicardial leads presumably represent the left ventricular ac-

tivation time in dogs, since this interval is always identical with or greater than the interval from the onset of the initial deflection to the peak of the R wave in left epicardial leads.\* That this interval showed no change after experimental production of left bundle-branch block in dogs (fig. 3) indicates that the left ventricular activation is still manifested by the same interval.

A clinical example of this situation is shown in figure 9, in which the patient developed left bundle-branch block as the result of a myocardial infarction. The block disappeared in about 1 month. In this instance, the time interval from the onset of the initial deflection to the nadir of the S wave in lead  $V_1$  remained identical in tracings obtained before and during left bundle-branch block and after its disappearance.

In 30 clinical cases of left ventricular hypertrophy 9 showed typical left bundle-branch block (figs. 7 and 8). The duration of the interval from the onset of the initial deflection to the nadir of the S wave in lead  $V_1$  was measured in all 30 tracings. It ranged from 0.045 to 0.080 second with a mean of 0.057 second (table 1). This duration is significantly longer than in normal subjects, in which the range was from 0.035 to 0.055 second, with a mean of 0.048 second. In these clinical cases without right ventricular hypertrophy, the prolonged duration of rS in lead  $V_1$  may be due to a hypertrophied left ventricle, or a diseased septum or both. The possibility that a diseased septum causes the prolonged rS interval was ruled out in the present experimental studies. The only possible cause for the increased time interval of rS is therefore hypertrophy of the left ventricle. Since the activation of the left ventricle appears to be manifested by the rS

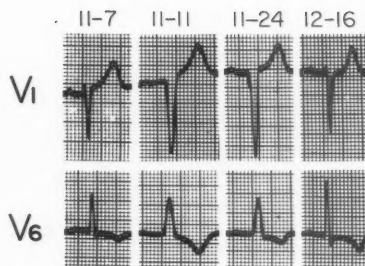


FIG. 9. Severe hypertension in a 53-year-old woman. The tracing on 11/7 shows typical left ventricular hypertrophy. The duration from the onset of the initial deflection in  $V_1$  to the nadir of the S wave is 0.07 second. The next tracing shows the QS pattern in  $V_1$  during the evolution of an acute myocardial infarction. In the same tracing, lead  $V_6$  shows an R pattern suggesting left bundle-branch block. An increase in the entire QRS duration is noted. The time interval from the onset of the initial deflection to the nadir of the S wave in lead  $V_1$  is the same as in the control tracing. The next tracing was taken during the convalescent stage. Again there was possible left bundle-branch block and no change in the duration of QS in  $V_1$ . On 12/16 the tracing became similar to that of the control, with no change in the duration of rS.

interval in lead  $V_1$ , not only in normal subjects but also in cases of left bundle-branch block, it follows that there is no delay in the onset of the left ventricular activation in the latter instances. This new concept differs markedly from the classic one.<sup>12</sup> The following alternative suggestions are offered to explain the mechanism of septal and ventricular depolarization in left bundle-branch block.

The septum may be activated from either direction or it may be activated simultaneously from right and left, depending upon the location and severity of the block in the left bundle. Whatever the direction of the initial septal activation may be, there is no delay in the arrival of the impulse at the subendocardial aspect of either ventricle. Therefore, depolarization of the free wall of the ventricles begins normally. At the same time, an abnormal potential occurs in the septum at the site of the block. Because of the location of the electrode in right ventricular leads, both epicardial and precordial leads register only the overwhelming potentials created by the nor-

\*The epicardial leads over the left ventricle of dogs appear to show a constant s wave. Which region of the heart causes this s wave is not clear. It may be the right ventricle near the pulmonary conus. The duration of rS in right epicardial leads of dogs seems to represent left ventricular activation time, but does not necessarily represent the activation time of the last portion of the heart to be depolarized.

mally activated ventricles, and the septal potentials are masked. The potentials derived from forces created by the activation of the free wall of the left ventricle produce a normal appearance of the rS wave in right ventricular leads. In contrast, left ventricular leads register the combined forces created by the normally activated ventricles and the abnormally activated diseased portion of the septum. Thus there occurs a slurring in the upstroke of the R wave. There is also a notch of the ascending limb of the R wave indicating the completion of the activation in the undiseased portion of the left ventricle. Simultaneous with the notch of the ascending limb of the R wave in left ventricular leads, the S wave in right ventricular leads inscribes its nadir as seen in normal tracings. The abnormal part of the septum then completes its activation and is followed by the activation of the portion of the left ventricle which is supplied by the diseased left bundle. These last forces appear to be directed toward the anterior portion of the heart<sup>10, 13</sup> rather than posteriorly, as in the normal heart. For this reason, the right ventricular leads register relatively positive potentials in the ascending limb of the S wave and a plateau in the R wave in left ventricular leads (fig. 8). This last force directed toward the anterior portion of the heart is often seen as a delayed positivity at the transitional area of clinical precordial leads (figs. 7 and 8).

This new concept, that the left ventricle begins its activation in a normal manner in cases of left bundle-branch block, is supported by the work of Braunwald and Morrow.<sup>14</sup> These investigators simultaneously catheterized both left and right ventricles in patients with left bundle-branch block. They found that the onset of both ventricular pressure curves occurred at the same instant. This observation is not compatible with the usual concept of left bundle-branch block, which postulates complete interruption of conduction in the left bundle, and tends to substantiate the new concept discussed above.

With this new concept it is possible to explain certain findings that have not been well

understood in the past, for example, the occurrence of a pure R wave in the left ventricular cavity lead in some cases of left bundle-branch block.<sup>5</sup> According to the classic theory,<sup>12</sup> the activation of the left ventricle always follows that of the septum. The inscription of an S wave in the left ventricular cavity lead is then expected, since the potentials are directed from within outward during the depolarization of the left ventricle and therefore register negative potentials. The absence of the S wave may be explained by the new concept as follows. Left ventricular activation begins in a normal manner. The activation of the blocked portion of the septum also starts about the same instant. Probably because of the location of the electrode in the left ventricular cavity, the septal potentials predominate in the cavity. In other words, the potentials created by the activation of the left ventricle do not produce any recordable negativity in the cavity, since its potentials are hidden in the positive deflection caused by the abnormally depolarized diseased septum. When the activation of the diseased septum takes more time than the normally activated left ventricle, there will be a continuous inscription of an R wave in the left ventricular cavity until the completion of activation of the diseased septum. The activation process then arrives at the portion of the left ventricular subendocardium that is supplied by the diseased portion of the left bundle. Normally, this potential associated with the depolarization of the blocked portion of the left ventricle would be recorded as an s wave in the cavity. However, if the blocked portion of the left ventricle is small, its potentials may be too weak to be recorded. Thus there may be no negativity inscribed as an s or S wave in some cases of left bundle-branch block. The size, location, and degree of severity of the block of the left bundle seem to be important in the inscription of a pure R wave in left ventricular cavity leads in some cases of left bundle-branch block.

The relationship between the nadir of the S wave in right ventricular leads and the peak of the R wave in left ventricular leads pre-

TABLE 2.—Duration of QRS Intervals in Normal Group and in Left Ventricular Hypertrophy

|   |           | Mean<br>(sec.) | Standard<br>deviation<br>(sec.) | p value |
|---|-----------|----------------|---------------------------------|---------|
| Duration of r in V <sub>1</sub> (from the onset of the r to its peak)   | Group I*  | 0.020          | 0.005                           |         |
|   | Group II* | 0.018          | 0.004                           |         |
| Duration of rS, qRS, and QS in V <sub>1</sub> (from the onset of the initial deflection to the nadir of the S wave) | Group I   | 0.048          | 0.006                           |         |
|   | Group II  | 0.057          | 0.008                           | <0.001  |
| Duration of qR and R in V <sub>7</sub> (from the onset of the initial deflection to the peak of the R wave)         | Group I   | 0.041          | 0.007                           |         |
|   | Group II  | 0.070          | 0.018                           | <0.001  |
| Duration of the widest QRS complex  | Group I   | 0.079          | 0.010                           |         |
|   | Group II  | 0.122          | 0.021                           |         |

\*Group I represents cases of normal individuals, and group II represents the present studies of left ventricular hypertrophy with and without left bundle-branch block.

sents an interesting problem. In normal human subjects and in normal dogs the nadir of S in V<sub>1</sub> always occurred simultaneously with or later than the peak of R in V<sub>7</sub> (figs. 1 and 2). In 23 of 30 cases of left ventricular hypertrophy the relationship was reversed: the nadir of S in V<sub>1</sub> occurred earlier than the peak of the R in V<sub>7</sub>. Rapaport and his associates<sup>15</sup> also found this relationship between the nadir of the S wave in right precordial leads and the peak of the R wave in left precordial leads in cases of left ventricular hypertrophy. They attributed these changes to rotation of the heart in association with left ventricular hypertrophy. Experimentally, however, this reversed relationship between the nadir of the S wave in right epicardial lead and the peak of the R wave in left epicardial lead was seen only when left bundle-branch block was produced.

It is postulated that an interpretation of findings of experimental studies may be applied to the precordial tracings in cases of left bundle-branch block. As long as the nadir of the S wave in lead V<sub>1</sub> coincides with or occurs later than the peak of the R wave in lead V<sub>7</sub>, the possibility of left bundle-branch block is most unlikely, regardless of the pattern or the duration of the entire QRS complex (fig. 4). Such instances may be classified as normal or left ventricular hyper-

trophy, depending upon the time interval from the onset of the initial deflection to the nadir of the S wave in V<sub>1</sub>. On the other hand, when the nadir of the S wave in lead V<sub>1</sub> occurs earlier than the peak of the R wave in lead V<sub>7</sub>, left bundle-branch block should be strongly suspected. In such cases, if the interval between the onset of the initial deflection in V<sub>1</sub> to the nadir of the S wave is increased, it is probable that left ventricular hypertrophy is also present.

To determine the statistical significance of the clinical studies, a t test was performed (table 2), comparing the mean of the time intervals from the onset of initial deflection to the nadir of S wave in V<sub>1</sub> and the time interval from the onset of initial deflection to the peak of R wave in V<sub>7</sub>. The p value was less than 0.001. This indicates that the former time interval is always shorter than the latter. The result is the reverse of that found in normal hearts.

These findings appear to provide a significant aid in the clinical diagnosis of left bundle-branch block. A larger group of cases, especially with pathologic correlation, is desirable further to substantiate the findings of the present studies.

#### SUMMARY AND CONCLUSIONS

Simultaneous tracings of right and left ventricular leads were made in 6 dogs with ex-

perimentally produced left bundle-branch block and in 30 clinical cases of left ventricular hypertrophy.

In the dogs the duration from the onset of the initial deflection to the nadir of the S wave in the right epicardial lead did not change after the experimental production of left bundle-branch block. On the other hand, there was a marked change in the configuration and duration of the left epicardial complexes.

After experimental production of left bundle-branch block, there sometimes occurred a delay in the onset of the initial deflection in leads obtained from the left ventricular cavity. The possible causes for this delay were discussed.

In patients with clinical left ventricular hypertrophy, the interval from the onset of the initial deflection to the nadir of the S wave in  $V_1$  was prolonged. This finding strongly suggests that this interval represents left ventricular activation time in cases of left ventricular hypertrophy, with or without associated left bundle-branch block.

The nadir of  $SV_1$  occurred earlier than the peak of  $RV_7$  only in cases of left bundle-branch block. This phenomenon appears to offer a useful criterion for the clinical diagnosis of left bundle-branch block.

It was concluded that in left bundle-branch block a considerable portion of the left ventricle begins its activation at the normal time and in a normal manner. Only that portion of the left ventricle supplied by the blocked part of the left bundle is depolarized later. This concept implies that complete functional block of the entire left bundle is doubtful, but that in practically all instances of left bundle-branch block, the block is incomplete.

#### ACKNOWLEDGMENT

The author wishes to express his gratitude to Drs. Gordon B. Myers and Harper K. Hellems, Detroit, Mich., to Dr. James Baer, Dearborn, Mich., and to Dr. Myron Prinzmetal, Los Angeles, Calif., for their valued advice and cooperation in the performance of this study. The author is also grateful to Dr. John Ord for his statistical analy-

sis and to Dr. Kouichi Tanaka for his assistance in writing the manuscript.

#### SUMMARY IN INTERLINGUA

Electrocardiogrammas simultanee a derivation dextero- e sinistro-ventricular esseva obtenite ab 6 canes con bloco de branca sinistre a production experimental e 30 casos clinic de hypertrophia sinistro-ventricular.

In le canes, le duration ab le declaration del deflexion initial usque al nadir del unda S in le derivation dextero-epicardial non se alterava post le production experimental de bloco de branca sinistre. Del altere latere, il occurreva marcate alterationes in le configuration e le duration del complexos sinistro-epicardial.

Post le production experimental de bloco de branca sinistre, il occurreva in certe casos un retardo in le declaration del deflexion initial in derivationes ab le cavitate sinistro-ventricular. Le causas possibile de iste retardo es discutate.

In patientes con clinic hypertrophia sinistro-ventricular, le intervallo ab le declaration del deflexion initial usque al nadir del unda S in  $V_1$  esseva prolongate. Iste facto es un forte indication que le intervallo in question representa tempore de activation sinistro-ventricular in casos de hypertrophia sinistro-ventricular, con o sin associate bloco de branca sinistre.

Le nadir de  $SV_1$  occurreva plus tosto que le zenit de  $RV_7$  solmente in casos de bloco de branca sinistre. Iste phenomeno pare representar un criterio de utilitate in le diagnose clinic de bloco de branca sinistre.

Esseva concludite que in bloco de branca sinistre, un portion considerabile del ventriculo sinistre comencia su activation al tempore normal e in un maniera normal. Dispolarisation retardate occurre solmente in le portion del ventriculo sinistre que es alimentate per le parte blockate del branca sinistre. Isto significa implicitemente que bloco functional complete del branca sinistre total es dubitose e que in practicamente omne casos de bloco de branca sinistre il se tracta de un bloco incomplete.

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**Scott, E. M., Griffith, E., Hoskins, D. D., and Whaley, R. D.: Serum-Cholesterol levels and Blood-Pressure of Alaskan Eskimo Men. *Lancet* 2:667 (Sept. 27), 1958.**

The Eskimo is often cited as a race which has little atherosclerosis, despite a high-fat diet. However, the incidence of atherosclerosis among Eskimos is actually unknown and many of them do not consume a high-fat diet. Accordingly, the serum cholesterol and blood pressure of 842 Eskimo men, age 17 to 53, were studied. The mean cholesterol level of 214.4 mg. per 100 ml. was not unusual. There was considerable variation of the mean depending on geographic location, northern Eskimos having higher levels than those of the south. The average systolic pressure was 126.9; the diastolic was 74.3 mm. Hg. Measurements of blood pressure showed much less variation.

KURLAND

# Studies of Fat Lipolysis by Post-Heparin Human Plasma Lipoprotein Lipase and by Human Pancreatic Lipase

By H. ENGELBERG, M.D.

Many studies indicate that unsaturated fats may lower serum cholesterol whereas saturated fats of animal origin usually increase it. The mechanism of these differing actions is unexplained, however. It has also been demonstrated that alimentary lipemia is cleared largely by an enzymatic lipolytic mechanism in which heparin is involved (heparin lipoprotein lipase). In this paper differences in hydrolysis of saturated and unsaturated fats by the heparin lipolytic factor are studied.

SINCE the original suggestion in 1941<sup>1</sup> there have been many studies recently summarized,<sup>2</sup> which indicate that relatively unsaturated oils of vegetable or marine origin may lower the serum cholesterol and low-density lipoproteins, whereas saturated animal fats usually increase the lipid values. This fact has aroused widespread interest because of its implications in the prevention of atherosclerotic disease. However, the metabolic factors underlying this differential effect of saturated and unsaturated fats are not well understood. It might be anticipated that fatty acid molecules varying in the number of hydrogen electrons attached to carbon would not behave identically in many biochemical interactions, some of which could profoundly affect serum lipid levels.

The problem has been investigated from various aspects. Both saturated and unsaturated fats are well absorbed in the human intestine.<sup>3-5</sup> The absorption of dietary cholesterol is augmented by unsaturated fats<sup>6, 7</sup> as compared to saturated ones. Thus it is apparent that the latter do not elevate plasma cholesterol by enhancing its absorption in the intestine. No difference has been found between the 2 types of fat in their effectiveness in depressing the ability of the liver to convert acetate carbon to fatty acids.<sup>8</sup> There has been disagreement among investigators who have studied the effect of various dietary fats on cholesterol synthesis in rat liver.<sup>9-13</sup> Similar amounts of choline were required to pre-

vent fatty livers when various fats were fed.<sup>14</sup> It has been stated that the ease of or resistance to hydrolysis of the cholesterol esters of saturated and unsaturated fats varies and that this, in some manner affects lipid transport.<sup>15</sup> Recently it was found that cholesterol-induced deposition of lipid in tissue cultures of human aorta cells is inhibited by linolenic acid and enhanced by stearic acid.<sup>16</sup> These results, however, do not explain the action of saturated fats in elevating circulating cholesterol levels. Furthermore, analysis of atheromatous plaques did not indicate any preferential deposition of saturated fats or of the cholesterol esters of saturated fats, although the linoleic acid content of the cholesterol esters was lower and the oleic acid level in the plaques higher than in normal sera.<sup>17-19</sup> The authors<sup>18</sup> interpreted their data as support for the concept that plaques are formed by filtration and indiscriminate deposition of blood lipids in the arterial wall. No evidence was found of any difference in the take-up of saturated or unsaturated fats by rat mesenteric adipose tissue.<sup>20</sup> In contrast to the previously cited studies, which do not explain the hypercholesterolemic effect of the saturated fats, recent investigations have shown an increased fecal excretion of bile acids or radioactive material fed as C<sup>14</sup> cholesterol coincident with the feeding of vegetable oils.<sup>21, 22</sup> Further studies along these lines in rat and man have clearly shown that the substitution of unsaturated for saturated fats results in an increased bile acid secretion in the bile and a fall in plasma cholesterol,<sup>2, 3, 7</sup> indicating an accelerated conversion of cholesterol to bile acids in the liver.

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Supported by grant H-2164 (C2) from the National Institutes of Health, U.S. Public Health Service.

TABLE 1.—*Unesterified Fatty Acid (U.F.A.) Release upon Incubation of Post-Heparin Plasmas with Ultracentrifugally Separated Lipoproteins after Cream and Safflower Oil, and with Activated Cream and Vegetable Oil Lipoproteins (Act. LP).*

| incubation<br>time at<br>37°C. (min.)          | 6 ml. Post-heparin plasma |                      | 7 ml. Post-heparin plasma |                      | 3 ml. Post-heparin plasma    |                                     |                                     |                                    |                                   |                              |
|--|---------------------------|----------------------|---------------------------|----------------------|------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-----------------------------------|------------------------------|
|  | 1 ml.<br>Saff. oil<br>LP  | 1 ml.<br>cream<br>LP | 1 ml.<br>Saff. oil<br>LP  | 1 ml.<br>cream<br>LP | 2 ml.<br>Cream<br>act.<br>LP | 2 ml.<br>Cott.<br>oil<br>act.<br>LP | 2 ml.<br>Olive<br>oil<br>act.<br>LP | 2 ml.<br>Coconut<br>oil act.<br>LP | 2 ml.<br>Peanut<br>oil act.<br>LP | 2 ml.<br>Corn oil<br>act. LP |
|  |                           |                      |                           |                      |                              |                                     |                                     |                                    |                                   |                              |
| 0  | 1.4                       | 2.0                  | .8                        | .9                   | 2.2                          | 2.1                                 | 2.8                                 | 1.8                                | 1.9                               | 1.8                          |
| 10   | 1.9                       | 1.9                  | 1.7                       | 1.4                  | 2.1                          | 2.0                                 | 3.2                                 | 1.9                                | 1.9                               | 1.9                          |
| 20   | 2.4                       | 2.0                  | 1.9                       | 1.6                  | 2.2                          | 2.1                                 | 3.3                                 | 2.4                                | 2.0                               | 1.9                          |
| 30   | 2.3                       | 2.1                  | 2.3                       | 1.6                  | 2.3                          | 2.4                                 | 3.1                                 | 2.4                                | 2.1                               | 2.0                          |
| Maximum rate<br>of lipolysis<br>in mEq./L./hr. | 3.0                       | .2                   | 5.4                       | 3.0                  | .2                           | .6                                  | 2.4                                 | 1.3                                | .4                                | .3                           |

Before this mechanism of action can be accepted as primarily responsible for the difference between the effect of animal and vegetable fats upon serum cholesterol, however, it should be realized that the level of cholesterol and bile acids in the bile may be secondary to other processes involved in fat metabolism and transport.

We have approached the problem of possible pathways whereby saturated and unsaturated fats might differ in their impact upon serum lipids by investigating their relation to the heparin lipemia-clearing system. A large body of evidence has been accumulating which indicates that alimentary lipemia is predominantly removed from the blood by an enzymatic lipolytic mechanism in which heparin plays a role. The neutral fat of the chylomera and the larger low-density or  $\beta$ -lipoproteins is split into fatty acids and glycerol, the fatty acids are bound to albumin, and then they are rapidly transferred from the blood to the tissues. It has been shown that albumin binds both oleic and stearic acid adequately.<sup>24</sup> It thus seems most unlikely that albumin would be a limiting factor in

this process except when it is markedly reduced, as in nephrosis. No difference has been found in the release of heparin into the blood, or in the production of lipemia-clearing factor following the oral ingestion of animal or vegetable fats.<sup>25</sup> Thus the 2 types of fat apparently affect this enzymatic mechanism to the same degree. However, the possibility existed that lipoproteins that contained predominantly saturated or unsaturated fats might differ in their rates of hydrolysis by the heparin lipolytic factor (lipoprotein lipase). It is known that fat substrates may vary in their susceptibility to lipolysis by the same enzyme.<sup>26, 27</sup> The experimental results presented in this paper are the preliminary findings relative to this subject.

#### METHODS

Clearing, or decrease in optical density, of fat substrates incubated in vitro was not studied, since this method of investigation may be deceptive. It does not always parallel lipolysis, the formation of calcium soaps may obscure optical density changes, and nonlipolytic clearing occasionally occurs. Lipolysis was not followed by glycerol measurements, since partial triglyceride splitting

TABLE 2.—*Rate of in Vitro Lipolysis of Cream and Cottonseed Oil Emulsions by Fasting Post-Heparin Plasma in Eleven Subjects. Incubation at 37°C.*

| Substrate                      | Maximum rate of free fatty acid release in mEq./L./hour<br>fasting post-heparin plasma 2-4 ml. |      |      |      |      |      |      |      |      |      |      |
|--------------------------------|--|------|------|------|------|------|------|------|------|------|------|
|                                | H.E.   | M.E. | H.B. | L.B. | B.W. | F.R. | A.G. | H.W. | B.M. | L.F. | L.T. |
| 2 dl. 5% Cream<br>emulsion     | .6   | 2.0  | 1.2  | 1.6  | 0    | 0    | .3   | .8   | 2.4  | 4.8  | .6   |
| 2 dl. 5% Cott.<br>oil emulsion | 3.0  | 3.6  | 4.8  | 3.0  | .6   | 1.2  | .8   | 3.3  | 1.8  | 3.0  | 1.6  |

TABLE 3.—Release of Unesterified Fatty Acid Upon Incubation of Citrate Eluates of  $\text{Ca}_3(\text{PO}_4)_2$  Adsorbates of Post-Heparin Plasma with Ultracentrifugally Separated Lipoproteins and Activated Lipoproteins of Animal and Vegetable Fat Origin

| Incubation time at 37 C. (min.)          | 2 ml. Citrate eluate                               |  | 2 ml. Citrate eluate + 3 ml. 1% $\text{CaCl}_2$ |                | 1 ml. Citrate eluate + 3 ml. 1% $\text{CaCl}_2$ |                |
|--|--|--|---|----------------|---|----------------|
|  | 5 ml. Serum preincubated with coconut oil emulsion | 5 ml. Serum preincubated with cream emulsion | 1 ml. Saff. oil LP                              | 1 ml. Cream LP | 1 ml. Saff. oil LP                              | 1 ml. Cream LP |
| 0  | 3.2  | 3.5  | 0.9   | 1.0            | 1.2   | 1.1            |
| 5  | 3.0  | 3.3  | 1.1   | 1.1            | 1.2   | 1.1            |
| 15                                       | 4.2  | 3.4  | 1.3   | 1.1            | 1.4   | 1.1            |
| 30                                       | 4.7  | 3.9  | 1.2   | 1.2            | 1.5   | 1.4            |
| Maximum rate of lipolysis in mEq./L./hr. | 4.0  | .8   | 2.4   | 1.2            | .8  | .6             |

|  | 2 ml. Citrate eluate + 2 ml. Bovine albumin        |  | 1 ml. Citrate eluate + 2 ml. 1% $\text{CaCl}_2$    |  |  |
|--|--|--|--|--|--|
|  | 3 ml. Serum preincubated with coconut oil emulsion | 3 ml. Serum preincubated with cream emulsion | 2 ml. Serum preincubated with coconut oil emulsion | 2 ml. Serum preincubated with coconut oil emulsion | 2 ml. Serum preincubated with cream emulsion |
| 0  | 1.4  | 1.8  | 3.2  | 2.7  | 2.9  |
| 10                                       | 1.8  | 1.7  | 3.4  | 2.6  | 3.0  |
| 20                                       | 1.9  | 1.9  | 3.4  | 2.7  | 3.0  |
| 30                                       | 2.0  | 2.1  | 3.6  | 2.8  | 3.2  |
| Maximum rate of lipolysis in mEq./L./hr. | 2.4  | 1.0  | 1.2  | .2   | .6   |

can take place without the production of free glycerol. Accordingly the rate of lipolysis was studied by determining the release of unesterified fatty acids. In general the plan of investigation involved the incubation *in vitro* at 37 C. of aliquots of plasma plus the various fat substrates. One-milliliter samples were removed at stated time intervals and analyzed (usually in duplicate) for free fatty acids by Borgstrom's method.<sup>28</sup> The maximal release of the latter in mEq./L./hour was then calculated from the maximal rate observed in any time period, since this is a more accurate measure of enzyme activity than the total release of unesterified fatty acids. This is particularly true in this *in vitro* test system in which the end-products of the reaction, the unesterified

fatty acids, are not removed and so inhibit further lipolysis.<sup>29</sup> Furthermore, it has been shown, with use of post-heparin plasma, that the concentration of lipemia-clearing factor is best determined by observations of the rate of clearing rather than by the absolute amount of optical density decrease in a fixed time period.<sup>30, 31</sup>

Since the lipolysis of various fats by the same enzyme was to be measured in all experiments it was essential to have little or no neutral fat present in the plasma other than the various substrates that were added *in vitro*. Therefore, the sources of lipoprotein lipase used were fasting post-heparin plasma (10 to 25 mg. intravenously) and citrate eluates of tri-calcium phosphate adsorbates of post-heparin nonfasting plasma.<sup>32</sup> Human pancreatic lipase was obtained from fresh autopsy material.<sup>6</sup>

Various types of fat substrates were used. When fasting post-heparin plasma was used as the enzyme source, 2 to 4 ml. of plasma were mixed with 2 ml. of 5 per cent emulsion in normal saline of the fats to be tested, thus providing adequate and equal amounts of fat substrate. Cream was used as the source of animal fat, since in this form it is well emulsified. It was bought in the market on the day it was to be tested as 35 per cent whipping cream, and diluted with saline to a 5 per cent solution. Commercial cottonseed oil was the usual vegetable fat used and it was prepared daily as a 5 per cent emulsion by the method of Tauber.<sup>33</sup> Although more stable emulsions resulted from the use of this method, it was our observation that the cream emulsions were superior to any of the vegetable fat emulsions. The plasma was then incubated with the fat emulsions. In this preparation lipoproteins were formed in the tube, and adequate fatty acid acceptor (albumin) and the necessary ions were in the plasma, so that all conditions were present for lipolysis to proceed. When pancreatic lipase was used, 1 per cent calcium chloride was added to provide fatty acid acceptor, and the various neutral fat emulsions themselves were excellent neutral fat substrates. In the experiments with citrate eluates of post-heparin plasma, preformed lipoproteins had to be used as fat substrate, since there was no opportunity for lipoprotein formation in the tube such as existed when plasma itself was directly used as the enzyme source. These activated lipoproteins were prepared *in vitro*<sup>34</sup> by prior incubation at 37 C. for 4 to 12 hours of cream and vegetable oil emulsions with equal volumes of fasting serum, or of infranatant serum obtained after ultracentrifugal removal of low-density lipoproteins.

\*Supplied through the cooperation of Dr. J. Friedman, and extracted by the Southern California Gland Company.

TABLE 4.—Release of Unesterified Fatty Acids upon Incubation of Two Lots of Human Pancreatic Lipase with Various Fat Substrates. Values in mEq./L.

| Incubation<br>time at 37 C.<br>(Min.)          | 1 ml. .05% Pancreatic lipase, 1 ml. 1% CaCl <sub>2</sub> |     |                                   |     |                                   |     |                                     |      |                                    |     |                                  |      |
|--|--|-----|-----------------------------------|-----|-----------------------------------|-----|-------------------------------------|------|------------------------------------|-----|----------------------------------|------|
|  | 5 ml. 5%<br>Cream<br>emulsion                            |     | 5 ml. 5%<br>Cott. oil<br>emulsion |     | 5 ml. 5%<br>Olive oil<br>emulsion |     | 5 ml. 5%<br>Coconut oil<br>emulsion |      | 5 ml. 5%<br>Peanut oil<br>emulsion |     | 5 ml. 5%<br>Corn oil<br>emulsion |      |
|  | 1  | 2   | 1                                 | 2   | 1                                 | 2   | 1                                   | 2    | 1                                  | 2   | 1                                | 2    |
| 0  | 1.5  | 1.5 | 1.6                               | 1.4 | 2.4                               | 1.9 | 2.1                                 | 1.6  | 2.1                                | 1.6 | 1.9                              | 1.6  |
| 10   | 1.5  | 2.0 | 2.7                               | 2.2 | 3.0                               | 3.4 | 3.3                                 | 3.8  | 3.3                                | 2.7 | 3.4                              | 3.4  |
| 20   | 1.9  | 2.5 | 3.2                               | 2.6 | 3.6                               | 4.0 | 4.5                                 | 4.8  | 3.6                                | 4.2 | 3.9                              | 3.8  |
| 30   | 2.2  | 3.0 | 3.2                               | 3.2 | 3.8                               | 3.7 | 5.8                                 | 7.0  | 4.4                                | 4.4 | 4.4                              | 4.0  |
| Maximum rate<br>of lipolysis<br>in mEq./L./hr. | 1.4  | 3.0 | 6.6                               | 4.8 | 3.6                               | 9.0 | 7.4                                 | 13.2 | 7.2                                | 7.8 | 9.0                              | 10.8 |

proteins. When used as fat substrate the "activated" lipoproteins prepared in vitro were not separated from the fasting serum with which they had been incubated. In addition low-density lipoproteins with differing neutral fat composition were separated ultracentrifugally<sup>10</sup> from serum samples obtained from the same subject after the ingestion of cream and safflower oil emulsion on different days. In the citrate eluate studies either bovine albumin or 1 per cent calcium chloride was added as fatty acid acceptor. In several experiments the in vitro activated lipoproteins were also used as fat substrate with post-heparin plasma or pancreatic lipase. The details of all experiments are found in the tables.

#### RESULTS

The findings with aliquots of fasting post-heparin plasma samples from 3 individuals plus various lipoprotein substrates are shown in table 1. In all 3 instances the rate of lipolysis of the unsaturated triglyceride lipoproteins was more rapid than that of the saturated (cream) lipoproteins. The method of calculation of the maximum rate of lipolysis is apparent from the data. At this time no comment will be made about comparisons in the rates of lipolysis of the various unsaturated vegetable oils as other experiments have not always shown similar results. However, the findings of lesser degrees of lipolysis with cream lipoproteins have been consistent. As shown in table 2, in 9 of 11 studies with aliquots of fasting post-heparin plasma plus

cream or cottonseed oil emulsions, the rate triglyceride splitting was faster when the unsaturated fat was the substrate. The results obtained with aliquots of citrate eluates of tricalcium phosphate adsorbates of nonfasting post-heparin plasma are outlined in table 3. In each of the 5 experiments the release of unesterified fatty acid was more rapid when the lipoprotein substrate was of vegetable oil origin. We have observed that when lipoproteins, either those prepared in vitro or in vivo, are over 1 week old, they may become unstable.

Tables 4 and 5 present the results of studies with human pancreatic lipase. In table 4 the fat substrates were neutral fat emulsions. The rate of hydrolysis of cream was lower than that of the vegetable oils with both batches of lipase. However, the results with the various oils as compared to one another were not consistent. As shown in table 5, with lipoprotein substrates and a larger amount of lipase, once again the saturated animal fat was split more slowly than the unsaturated vegetable fat.

Toward the conclusion of these investigations a serious complicating factor was recognized, which perhaps should have been anticipated, namely, the occasional activation of lipases contained in the fats themselves upon the addition of fatty acid acceptors. Also, rarely, there was a sudden release of fairly large amounts of free fatty acid that apparently represented a nonenzymatic disruption of triglyceride. Both these sources of error occurred much more frequently with cream

Both the infranatant serum and the ultracentrifugally separated cream and safflower oil lipoproteins were obtained through the cooperation of Mr. D. Spector of the Institute of Medical Physics, Belmont, Calif.

TABLE 5.—Unesterified Fatty Acid Release upon Incubation of Human Pancreatic Lipase with Cream and Vegetable Oil Lipoproteins. Values in mEq./L.

| Incubation time at 37 C. (min.)          | 2 ml. Pancreatic lipase 3 ml. 1% CaCl <sub>2</sub> |                       | Incubation time at 37 C. (min.) | 2 ml. Pancreatic lipase 3 ml. 1% CaCl <sub>2</sub> |                       |
|--|--|-----------------------|---------------------------------|--|-----------------------|
|  | 2 ml. Cott. oil lipoprot.                          | 2 ml. Cream lipoprot. |                                 | 1 ml. Saff. oil lipoprot.                          | 1 ml. Cream lipoprot. |
| 0  | 1.9  | 2.0                   | 0                               | 1.3  | 1.3                   |
| 5  | 2.2  | 2.1                   | 10                              | 1.8  | 2.1                   |
| 15                                       | 5.1  | 2.6                   | 20                              | 3.5  | 2.9                   |
| 30                                       | 17.7   | 4.0                   | 30                              | 3.6  | 3.5                   |
| Maximum rate of lipolysis in mEq./L./hr. | 31.6   | 4.0                   |                                 | 6.6  | 4.8                   |

than with cottonseed oil. Table 6 shows several examples of the action of endogenous lipases in the fats. It may be that the results in patients B.M. and L.F. in table 2 were not entirely due to lipoprotein lipase activity. It is improbable that when a fat emulsion is added to plasma *in vitro*, the entire neutral fat content becomes incorporated into lipoproteins in a few minutes. Furthermore lipoproteins themselves may be degraded nonenzymatically.<sup>35</sup>

#### DISCUSSION

A large amount of evidence has accumulated which indicates that the heparin-lipoprotein lipase enzyme system is probably the major normally functioning pathway for the removal of alimentary neutral fat from the blood. Thus any major distinction in the activation of this mechanism by the various types of fat, or in the efficiency of lipolysis of the fats by the enzyme, would be of importance in determining the effect of the ingested fat upon serum lipid levels. In previous studies<sup>25</sup> no difference was found in the stimulation of heparin production or of lipemia-clearing activity by animal and vegetable fats. The present data indicate that the lipolysis of unsaturated triglyceride lipoproteins by lipoprotein lipase is more rapid than that of the saturated variety. Since these experiments were performed *in vitro*, variations in the rate of absorption, in tissue take-up of fatty acids, in liver function in relation

TABLE 6.—Release of Unesterified Fatty Acid upon Incubation of Cream and Cottonseed Oil Emulsions Plus Fatty Acid Acceptor

| Incubation time at 37 C. (min.)          | 4 ml. Cream emulsion + 1 ml. bov. alb. |  | 4 ml. Cott. oil emulsion + 1 ml. bov. alb. |  | 5 ml. Cream emulsion + 1 ml. 1% CaCl <sub>2</sub> |  | 5 ml. Cott. oil emulsion + 1 ml. 1% CaCl <sub>2</sub> |  |
|--|--|--|--|--|---|--|---|--|
|  |  |  |  |  |   |  |   |  |
| 0  | 4.0                                    |  | 3.5  |  | 1.9   |  | 1.8   |  |
| 10                                       | 4.3                                    |  | 3.6  |  | 1.9   |  | 1.8   |  |
| 20                                       | 4.3                                    |  | 3.7  |  | 2.1   |  | 1.8   |  |
| 30                                       | 4.4                                    |  | 3.6  |  | 2.0   |  | 1.8   |  |
| Maximum rate of lipolysis in mEq./L./hr. | 1.8                                    |  | .6   |  | .6  |  | 0   |  |

to fats and cholesterol, in bile acid or cholesterol excretion, in reticuloendothelial phagocytosis of lipid particles, played no part in the results.

The similar findings with use of human pancreatic lipase fortify the conclusion that triglycerides composed of fatty acids of essentially the same chain length, but of different degrees of unsaturation, vary in their susceptibility to lipolysis by fat-splitting enzymes. Previous workers have found that rat pancreatic lipase is more active on saturated fats than on those with a high degree of unsaturation.<sup>36, 37</sup> On the other hand, with pork pancreatic lipase, the number of unsaturated bonds (0 to 2) did not affect the speed of hydrolysis.<sup>38</sup> Apparently species differences in pancreatic lipase selectivity do exist. This question has not been investigated in animals with use of the post-heparin enzyme.

It may be argued that the various lipoprotein substrates used in these experiments were unnatural. Thus ultracentrifugally separated low-density lipoproteins may have been altered in some way by the involved procedure. The "activated" lipoproteins were prepared *in vitro*, as were the lipoproteins that formed when the fat emulsions were added to plasma.

There is little reason, however, to believe that these substrates are substantially different in their differential susceptibility to hydrolysis from their circulating counterparts. Also the efficiency of the emulsifier

tion procedure and the stability of the emulsion could influence enzyme activity. It has been our experience that cream is a better and more stable fat emulsion than the artificial vegetable oil emulsions we prepared. If anything this factor would have prejudiced the results in favor of animal fats as the preferential substrate, whereas the findings were quite the opposite. Finally it is possible that lipoprotein formation of substrate for lipoprotein lipase would be more rapid with the unsaturated fats. However, there is no evidence supporting this possibility. Various studies of chylomicron composition after animal fat intake have shown the presence of a protein component very soon after the entry of the lipid particles into the blood stream.

There are good grounds for believing that high-density or  $\alpha$ -lipoproteins, which are higher in their cholesterol content than the large low-density particles, function as carrier molecules for neutral fat in the blood stream. It is probable, therefore, that when the plasma neutral fat content is lower, because of its more rapid lipolysis and subsequent exit to the tissues, less cholesterol need be discharged into the blood as a component of the high-density lipoprotein molecule. Cholesterol may then be converted into bile acid by the liver and excreted in the bile. Thus the effect of unsaturated fats in reducing blood cholesterol and increasing bile acid secretion<sup>21-23</sup> may not have been due to a direct action upon bile acid formation by the liver, but instead may represent a secondary consequence of the more rapid removal of unsaturated triglyceride from the blood.

#### SUMMARY

The rate of lipolysis of vegetable fat lipoproteins by human post-heparin lipemia-clearing factor was more rapid than that of animal fat lipoproteins in nearly all experiments.

Similar results were obtained with human pancreatic lipase as the fat-splitting enzyme.

The more efficient activity of heparin lipoprotein lipase upon unsaturated fat substitutes may account for the hypercholesterol-

emic and hyperlipoproteinemic effect of animal (saturated) fats in man.

#### SUMMARIO IN INTERLINGUA

Le intensitate del lipolyse de lipoproteinas de grassia vegetal per human factor de clearance de lipemia post uso de heparina esseva plus grande que le intensitate del lipolyse de lipoproteinas de grassia animal in quasi omne le experimentos del presente studio.

Simile resultatos esseva obtenite con le uso de human lipase pancreatic como enzima lipolytic.

Le plus efficace activitate de lipase de lipoproteina post heparina in substratos de grassia nonsaturate explica possiblementemente le effecto hypercholesterolemie e hyperlipoproteinemic de grassias animal (saturate) in humanos.

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## Extrapulmonic Stenosis of the Pulmonary Veins

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**P**ULMONARY venous stenosis is a rare condition. A case combining unilateral stenosis and atresia was included by Ferencz and Dammann<sup>1</sup> in a series of congenital abnormalities associated with pulmonary venous obstruction. The abnormality occurred in a child who developed severe recurrent hemoptysis at 1½ years of age and thereafter suffered from progressive dyspnea and orthopnea. The patient exhibited right heart failure with pulmonary arterial hypertension. Death occurred at the age of 2½ years. Post-mortem examination disclosed atresia of the vein from the lower lobe and stenosis of the vein from the left upper lobe; the right pulmonary veins were normal. Arteriolar sclerosis was restricted to the left lung.

Bilateral obstruction was reported by Reye<sup>2</sup> in the case of an 8-year-old girl, who was thought to have had congenital heart disease and who terminally developed right heart failure. She had stenosis of the veins from the left upper and lower and the right lower lobes. The vein from the right upper lobe was atretic.

The only comparable cases encountered in a review of the literature were those reported by Aust,<sup>3</sup> Romberg,<sup>3</sup> Posselt,<sup>4</sup> and Hart<sup>5</sup> as "primary" pulmonary arteriosclerosis. In these 4 cases in young adults, pulmonary arteriosclerosis was associated with diminution in caliber of the pulmonary veins and hypoplasia of the left side of the heart. Both Posselt and Hart thought that the venous abnormality was congenital, and Posselt attributed it to a form of fetal endocarditis. The onset of the disease in adult life would lead one to suspect, however, that the hypoplasia of the left ventricle and aorta and possibly the apparent constriction of the pulmonary veins

were only relative to marked hypertrophy and dilatation of the right ventricle and dilatation of the pulmonary artery.

In the case reported below, marked constriction of all the pulmonary veins appeared to be the primary factor in the development of severe pulmonary arterial hypertension.

### CASE REPORT

The patient was a 6-year-old Negro boy admitted to Children's Hospital of Michigan because of recurrent hemoptysis.

During the first 4 years of life the child had occasional respiratory infections. At 4 years of age a chest roentgenogram revealed cardiac enlargement and an electrocardiogram right ventricular hypertrophy. Later the child had repeated episodes of hemoptysis, which became progressively more severe and for which he was hospitalized. Angiocardiographic studies showed dilatation of the pulmonary artery and its major branches but no evidence of cardiovascular malformation (fig. 1). Bronchoscopic examination was initially negative, but on subsequent examination very hyperemic, "granulomatous" tissue was seen partially occluding the right upper lobe bronchus. A thoracotomy was undertaken and abnormally vigorous pulsations were present in the azygos and intercostal veins. A faint thrill, which could be obliterated by occluding the pulmonary artery, was present in the right upper lobe. This lobe was firmer than the others and was resected. Pathologic examination of the specimen revealed extensive arterial and venous thrombosis in varying stages of organization.

At 6 years of age, when he was readmitted because of increasing dyspnea, fatigue, and fever, he was slightly cyanotic with tachypnea and moderate dyspnea. Venous distention was present in the neck. Rales were heard and breath sounds were decreased in the left upper chest. The blood pressure was 100/40 mm. Hg and the pulse rate 144 per minute. A rumbling systolic and a soft diastolic murmur were heard at the apex. The pulmonary second sound was booming in character. A continuous hum was heard to the right of the sternum in the second intercostal space. The liver was felt 5 to 6 cm. below the costal margin in the right midclavicular line. It was smooth, firm, and quite tender. Laboratory data included a hemoglobin of 9.4 Gm. per 100 ml. and a red

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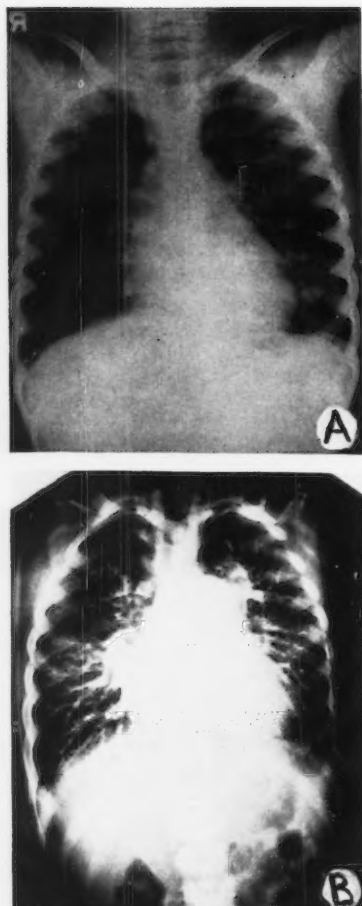


FIG. 1. A. Posteroanterior film, just prior to onset of illness, showing a relatively normal heart size with normal pulmonary vascularity and clear lungs. B. Angiocardiogram demonstrating marked dilatation of the main pulmonary artery and the hilar branches. Other films in study showed normal peripheral vascularity.

blood cell count of 3,080,000 per mm.<sup>3</sup> A roentgenogram of the chest revealed further enlargement of the heart (11.3/18.8 cm.), rather marked prominence of the pulmonary artery segment along the left sternal border, vascular congestion of both lungs, and parenchymal infiltration of the left upper lobe. An electrocardiogram revealed a marked increase in the right ventricular hypertrophy pattern and nonspecific myocardial changes.

The patient was placed in oxygen and treated with digitalis and antibiotics. His temperature stabilized between 99 and 100 F. orally, his heart

rate fell to 86 to 92 per minute, and the liver was no longer palpable. He was more comfortable, but his cough was occasionally productive of considerable amounts of bright red blood. Approximately 1 month after admission he suddenly developed marked left anterior chest pain, rapidly rising temperature, profuse diaphoresis, cyanosis, and tachypnea. The patient died four hours after the onset of these symptoms.

At postmortem examination the heart was greatly enlarged and weighed 280 Gm. (normal weight approximately 95 Gm.). The right atrium and ventricle were greatly dilated and hypertrophied. The pulmonary artery was wide and presented atheromatous plaques on its intimal surface. There was dilatation of the left side of the heart in association with slight ventricular hypertrophy, and a moderately severe degree of endocardial sclerosis was present in the left atrium. There was no evidence, grossly or microscopically, of mural thrombosis to account for the endocardial thickening. The 3 remaining pulmonary veins were stenotic at their respective junctions with the left atrium. On the left, the 2 veins entered separately, and the lumen of each was only 1 to 2 mm. in diameter (fig. 2B). The atrial endocardium around the venous orifices was greatly thickened, and there was marked intimal sclerosis of the veins. On the right, the vein from the upper lobe had been ligated when the lobe was removed, and the vein from the lower lobe was both stenotic and partially occluded by an organizing thrombus (fig. 2A). The thrombus appeared to have resulted from the ligation of and marked proliferative reaction around the stump of the upper vein. Microscopic examination of the heart revealed, in addition to myocardial hypertrophy, a very slight ventricular infiltrate of mononuclear cells, insufficient to warrant the diagnosis of myocarditis. There were, however, prominent intimal fibrosis and moderate medial hypertrophy of the branches of both coronary arteries. There was no obvious relationship between the changes in the coronary arteries and those in the left atrium, unless both were the result of a common inflammatory process. The ventricular endocardium, on the other hand, was only minimally thickened.

The pulmonary changes were striking, and most prominent among them were innumerable arterial thrombi in all stages of organization and recanalization. The large arteries contained grossly visible, usually white thrombi, which partially occluded the lumina; the lumina distal to the thrombi were frequently dilated. The thrombi extended into the smallest vessels (fig. 3A) and were associated with focal necrosis and irregular areas of hemorrhage and organizing pneumonitis. The degree of connective tissue proliferation exceeded



FIG. 2. Stenosis of the pulmonary veins at their junction with the left atrium: *A*. Right lower vein admits only fine needle; occlusion of upper vein and adventitial fibrosis secondary to surgical ligation. *B*. Localized constriction in left upper vein admitting black thread.

that usually seen in pulmonary infarction, but the reaction was conspicuously bland. It was apparent microscopically that some of the thrombosed vessels were veins (fig. 3*C*), and in a few areas there were necrosis and inflammatory cell infiltration of arterial walls (fig. 3*D*). Extremely dilated bronchial vessels, approximating varices, appeared to represent collateral circulation, and the bronchial arteries had thickened walls (fig. 3*E, F*). No extrapulmonic source of emboli was found, and the inflammatory arterial changes are regarded as hypertensive. Intimal sclerosis was present in the arterioles and seemed to be due in good measure to the recanalization of thrombi (fig. 3*A*). Medial hypertrophy of the small vessels existed both together with and apart from the intimal fibrosis (fig. 3*B*).

In summary, there was extrapulmonic stenosis of the pulmonary veins, in association with pulmonary arteriolar sclerosis and pulmonary arterial and venous thrombosis. A marked degree of cor pulmonale was present and was associated with hypertensive pulmonary arteritis.

#### DISCUSSION

Structural alterations in the pulmonary vascular system are commonly associated with and attributed to sufficiently prolonged and severe obstruction to the flow of blood from the lungs through the left side of the heart. Gross dilatation and sclerosis<sup>4</sup> and microscopic alteration<sup>6</sup> of the pulmonary arteries have long been recognized as an accompaniment of acquired mitral stenosis, and as early

as 1927 Moscheowitz<sup>7</sup> singled out hypertension of the lesser circulation as the factor common to cases of pulmonary arteriosclerosis associated with both obstructive lesions in either the heart or lungs and vascular shunts in either the heart or great vessels. Congenital mitral stenosis,<sup>1</sup> cor triatriatum with stenosis of either the common pulmonary vein<sup>8</sup> or intrapulmonary veins,<sup>9</sup> constrictive endocardial sclerosis,<sup>10</sup> tumors of the left atrium,<sup>11</sup> and extrinsic pressure on the pulmonary veins<sup>12</sup> have all been related to the development of pulmonary arterial and arteriolar sclerosis.

In the case of acquired mitral stenosis some evidence has been offered that the extent of the vascular changes in the lungs correlates with the severity of the obstruction at the mitral valve<sup>13</sup> and the duration<sup>14</sup> and degree<sup>15, 16</sup> of pulmonary hypertension, and that severe hypertension may lead to vascular necrosis in the lungs.<sup>13, 17-20</sup> Other evidence, both clinicopathologic<sup>21</sup> and experimental,<sup>22</sup> has been adduced to show that increased resistance and pressure are due to reversible vascular spasm, and that anatomic changes in the pulmonary vessels are largely the result of thromboembolic phenomena, even in association with obstruction of the pulmonary venous flow.

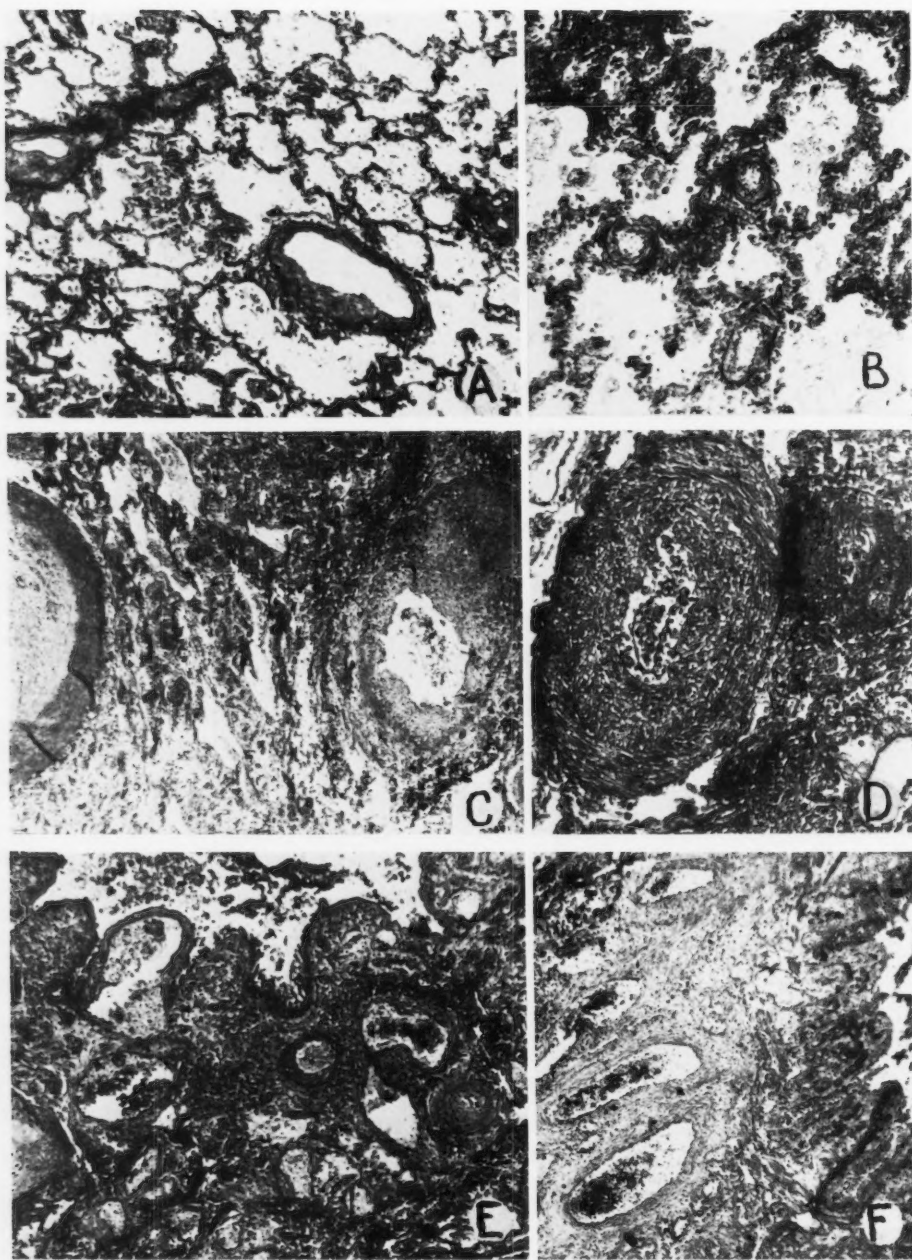


FIG. 3. *A.* Intimal fibrosis in arterioles and small pulmonary arteries. Verhoeff elastin stain. *B.* Medial hypertrophy or muscularization of arterioles. Verhoeff elastin stain. *C.* Organizing arterial (*left*) and venous (*right*) thrombosis; intervening area of chronic inflammation and fibrosis. Hematoxylin and eosin stain. *D.* Acute arteritis with inflammatory cell infiltrate in wall. Hematoxylin and eosin stain. *E.* Dilated, thick-walled vessels in bronchial mucosa. Hematoxylin and eosin stain. *F.* Venous varices in bronchial wall. Mallory aniline blue stain.

The alterations in arterioles and small arteries are generally compounded of medial hypertrophy and intimal fibrosis or proliferation. The former may reasonably be attributed to increased vascular tension, and although the problem of persistence of fetal vascular structure need not concern us here there seems to be ample evidence for muscularization of arterioles and medial hypertrophy in response to obstruction of the pulmonary venous flow.<sup>15, 23, 24</sup> Intimal fibrosis in the smaller vessels has also been regarded as a consequence of pulmonary hypertension.<sup>15, 24</sup> In the case reported herein, the intimal thickening is irregular and seems to have arisen at least in part from thrombosis and recanalization of the smaller vessels. The presence of such widespread thrombosis is regarded as a direct complication of hypertension and vascular sclerosis, possibly mediated by an arteritis, rather than as an embolic phenomenon.

The development of arteritis in this case must be regarded as the consequence of hypertension. Inflammatory lesions occurred independently of thrombi, although they may have preceded them. In several areas there appeared to be a healing or healed arteritis, but "fibrinoid" necrosis of the very small vessels was not seen.

The venous thrombi present an unusual complication that is not easily explained. Previously described instances of pulmonary venous thrombosis in association with pulmonary thrombophlebitis<sup>25</sup> and primary vascular sclerosis,<sup>26</sup> or as an anatomic finding in infants dying unexpectedly<sup>27</sup> offer little to the understanding of this case. In the case reported by Schonlebe<sup>28</sup> of a 4-month-old child with endocardial sclerosis and pulmonary venous thrombosis there were also transposition of the great vessels, pulmonary stenosis, and an interventricular septal defect. It is possible that the venous thrombosis in our case may have been enhanced by stasis due to obstruction at both ends—arterial thrombosis and venous stenosis—but there is no direct evidence to support this view. The alternate supposition that venous thrombosis led to phlebosclerosis and constriction does not make the case any more plausible or less

unique. In the case of a young child who developed diffuse interstitial fibrosis of the lungs during infancy, reported by Diamond<sup>29</sup> as a case of Hamman-Rich syndrome, there were extreme constriction of the pulmonary artery and vein and severe arteriolar sclerosis in one lung. Complete constriction of the pulmonary vein was present at its junction with the left atrium, and because of the inflammatory process in the lungs and the hilar adventitial tissue the abnormality of the vessels was attributed to inflammation and scarring rather than to a congenital malformation. More than a slight degree of pulmonary inflammation was not seen in our case and significant scarring in the hilar structures was limited to the stump of the right upper lobe vein.

More satisfactory is the view that the venous stenosis, uncommon as it might be, was the primary factor in the development of pulmonary hypertension and vascular disease. The 2 cases cited above<sup>1, 2</sup> combined stenosis and atresia, indicating that the abnormality was a congenital malformation. Despite the age of the patient and the relatively late onset of symptoms in our case, the abnormality might still be regarded as congenital. The clinical course suggests that it may have been progressive, and possibly it bore some relationship to the endocardial sclerosis of the left atrium and to the intimal changes in the branches of the coronary arteries. However, as commonly as we see involvement of the left atrial endocardium in both primary and secondary endocardial sclerosis we have not seen it associated with pulmonary venous stenosis in either reported<sup>30</sup> or observed cases. Indirect evidence in support of venous obstruction was the early development of extensive collateral circulation. Hemoptysis, the initial complaint, appears to have been due to bleeding from bronchial mucosal varices, a condition similar to that seen in acquired mitral stenosis.<sup>31</sup> At the time of the pulmonary resection there were abnormally dilated, pulsating azygos veins. Arterial and venous thrombosis was seen in the resected portion of lung, but the initial cause of venous obstruction could not be determined.

## SUMMARY

A case is reported of a 6-year-old boy who had developed pulmonary hypertension because of obstruction to the pulmonary venous flow by severe stenosis of the pulmonary veins at their junction with the left atrium. The development of collateral circulation through the bronchial vessels led to early, severe hemoptysis. The course was complicated by the development of pulmonary arterial and venous thrombi and hypertensive arteritis.

## ACKNOWLEDGMENT

The authors are indebted to Mr. Charles L. Zinser for the photographs and photomicrographs.

## SUMMARIO IN INTERLINGUA

Es reportate le caso de un puero de 6 annos de etate qui habeva disveloppate hypertension pulmonar in consequentia de obstruction del fluxu pulmono-venose per sever grados de stenosis del venas pulmonar al sito de lor junction con le atrio sinistre. Le disveloppamento de un circulation collateral via le vasos bronchial resultava tosto in sever hemoptysis. Le curso clinic del caso esseva complicate per le disveloppamento de thrombos pulmono-arterial e -venose e arteritis hypertensive.

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Thomas, C. B., and Murphy, E. A.: Further Studies on Cholesterol Levels in the Johns Hopkins Medical Students: The Effect of Stress at Examinations. *J. Chron. Dis* **8**:661 (Dec.), 1958.

In a study of the effects of stress on serum cholesterol levels, the serum cholesterol, total circulating eosinophils, body weight, blood pressure, and heart rate were measured at 3 different periods that were associated with varying degrees of stress. The first set of data was collected 3 weeks after starting the first year course in anatomy, the second set at the time of the final examination period in anatomy which was felt to be the period of maximal stress, and the final set of data was collected at a varying interval after the anatomy examination period at the convenience of the subject. Subjects were 52 male first-year medical students. The highest mean cholesterol value was found to occur at the time of the anatomy examination. It was 225.7 mg./100 ml. It was significantly greater than the value of 204.7 mg./100 ml. found at the examination made at random with presumably little stress. The mean cholesterol level of 224.4 mg./100 ml. found 3 weeks after starting medical school was not significantly lower than the value at the time of the anatomy examination. The mean eosinophil count at the time anatomy examination was 97 per cm.<sup>3</sup> while at the time of the third or random examination the mean was 129 per cm.<sup>3</sup> which was thought to be a significant difference. The measurements of pulse rate and systolic and diastolic blood pressures showed a significant difference only in the measurement of the diastolic blood pressure, which was highest at the time of the anatomy examination, next highest at the time of the initial examination, and lowest at the time of the random examination. Variations in body weight were effectively excluded as a cause for variation in cholesterol levels.

MAXWELL

# An Evaluation of the Nitrous Oxide Method for the Quantification of Left-to-Right Shunts

## An Experimental Comparison of the Gasometric Technic with Directly Metered Blood Flows

By RICHARD J. SANDERS, M.D., THEODORE COOPER, M.D., PH.D., AND  
ANDREW G. MORROW, M.D., F.A.C.S.

Extensive clinical use has now been made of the nitrous oxide test for the detection and localization of left-to-right circulatory shunts. On theoretical grounds the magnitude of such a shunt should be related to the systemic and pulmonary arteriovenous differences in nitrous oxide content measured early in the period of inhalation. In order to determine the validity of the nitrous oxide method for the quantification of a left-to-right shunt, total pulmonary and shunt flows were directly measured in experimental animals as nitrous oxide tests were performed simultaneously.

UNTIL METHODS are available for the direct measurement of total pulmonary and systemic blood flows in the intact patient, the clinical physiologist must rely upon estimates of their magnitude obtained by various indirect means. Many forms of congenital heart disease are associated with an abnormal intracardiac or extracardiac communication resulting in a left-to-right circulatory shunt and a pulmonary blood flow in excess of the systemic. Since the majority of such conditions may now be corrected, intelligent pre-operative evaluation should include precise localization of the defect and a reliable estimate of the blood flow through it. The ratio of pulmonary to systemic blood flow is most commonly determined by relating the arteriovenous differences in oxygen content in the 2 circulations.<sup>1, 2</sup> The application of indicator-dilution technics for this purpose has been recently summarized by Wood and his co-workers.<sup>3, 4</sup> Clinical studies with nitrous oxide and the radioactive gas krypton<sup>5</sup> have shown that the large arteriovenous difference that exists shortly after the onset of inhalation of such inert gases may also be used to estimate the ratio of pulmonary to systemic flow and the relative magnitude of a left-to-right shunt.<sup>5-7</sup>

The present study was designed to assess the reliability of the nitrous oxide method for the quantification of left-to-right shunts, by comparing the results of this technic with those obtained with directly metered blood flows in the experimental animal.

### METHODS

Mongrel dogs, weighing 11 to 25 Kg. were anesthetized with intravenous thiopental and ventilated with 100 per cent oxygen except during nitrous oxide tests. Polyethylene catheters were inserted into each femoral artery and into the right atrium for pressure recordings and blood sampling. Following endotracheal intubation, a left thoracotomy was performed, and the left fourth and fifth ribs were removed. The left and right pulmonary arteries were freed extrapericardially and the left pulmonary artery was divided 1 cm. distal to its origin. Heparin (3 to 5 mg./Kg.) and digoxin (0.1 mg./Kg.) were given intravenously after completion of the dissection. The proximal and distal ends of the left pulmonary artery were then cannulated with Tygon tubing of 1-cm. internal diameter and circulation was reestablished through a flow meter, as shown diagrammatically in figure 1. Intermittent diversion of the total pulmonary flow through the flow meter could then be accomplished by occlusion of the right pulmonary artery with a ligature. A left-to-right shunt was created by connecting the left subclavian and brachiocephalic arteries to the pulmonary circuit through a second flow meter (fig. 1). The magnitude of the shunt was regulated by adjustment of a screw clamp on the

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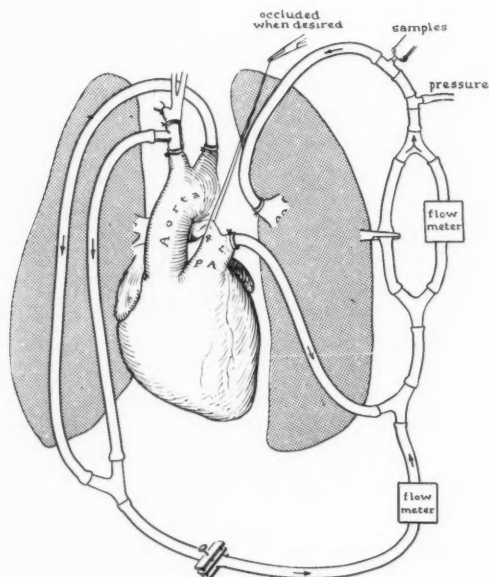


FIG. 1. Schematic representation of the method employed for the direct measurement of total pulmonary flow and left-to-right shunt flow in the dog.

tubing. It was frequently found desirable to support or alter the systemic pressure by intravenous infusion of a solution of norepinephrine (8 mg./L.).

Total pulmonary flow and shunt flow were measured with 2 electromagnetic blood flow meters,<sup>8</sup> which were adjusted to record identical deflections for equal rates of flow. The stability of each meter was often checked and zero flows were recorded frequently during each experiment without interruption of the total pulmonary flow by appropriate manipulation of the accessory "bypass" line around the flow meter (fig. 1). In each dog the 2 meters were simultaneously calibrated by opening the shunt line and occluding the left pulmonary artery while the right pulmonary artery remained open. A given quantity of blood could thus be directed from the shunt through both meters into a graduated cylinder during a measured time interval. Figure 2 illustrates a typical standardization of the 2 meters both before and after the shunt and total pulmonary flows were measured. The calibrations of the flow meters did not vary in their reproducibility by more than 5 per cent on any occasion.

Pulmonary and systemic arterial pressures were measured by means of Statham P-23A and P-23D pressure transducers. Both pressures and flows

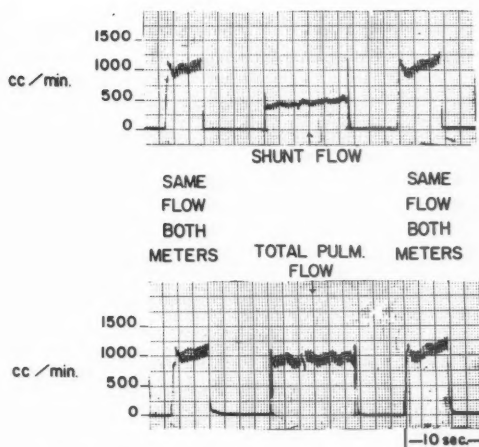


FIG. 2. Record illustrating the method for simultaneous calibration of the 2 meters with and without flow before and after the measurement of total pulmonary flow and shunt flow (center of tracing).

were recorded on a direct-writing multichannel oscillograph. The mean pressures and flows during the periods of sampling were obtained by planimetric or electronic integration of the records.

Nitrous oxide tests were performed by ventilating the dogs with a gas mixture containing 50 per cent nitrous oxide and 50 per cent oxygen or 100 per cent nitrous oxide for 30 seconds. Between the tenth and thirtieth seconds of inhalation, integrated blood samples were drawn simultaneously from the femoral artery, the right atrium, and from the pulmonary artery distal to the entrance of the shunt (fig. 1). A sample for nitrogen blank determination was always obtained immediately prior to each test. The nitrous oxide contents of the right atrial and pulmonary arterial samples were expressed as percentages of the corresponding femoral arterial samples,  $\frac{RA \text{ or } P 1}{Art.}$

$\times 100 = \%$ . Only those samples obtained during a steady state, as indicated on the flow meter records, were included in the series.

The blood samples were drawn into oiled, heparinized syringes which were closed with mercury-filled caps, and their nitrous oxide content was determined manometrically.<sup>9</sup> Duplicate determinations were frequently carried out to determine the analytic error, which never exceeded 0.2 vol. per cent.

#### RESULTS

The results of 18 nitrous oxide tests and the metered blood flows during the respective sampling periods of each test are summarized

TABLE 1.—*Pulmonary to Systemic Flow Ratios Determined from Simultaneous Nitrous Oxide Tests and Metered Blood Flows*

| Dog no. | Weight Kg. | Metered flows               |                      |                          |                       | N <sub>2</sub> O tests |           |           |         |          |                       | Mean pressures (mm. Hg) |    |
|---------|------------|-----------------------------|----------------------|--------------------------|-----------------------|------------------------|-----------|-----------|---------|----------|-----------------------|-------------------------|----|
|         |            | Total pulm. flow (ml./min.) | L-R shunt (ml./min.) | Systemic flow (ml./min.) | Pulm. flow syst. flow | Samples                |           |           | Ratios  |          | Pulm. flow syst. flow | FA                      | PA |
|         |            |                             |                      |                          |                       | FA* Vol. %             | PA Vol. % | RA Vol. % | PA/FA % | RA/FA† % |                       |                         |    |
| 3       | 19.1       | 1320                        | 850                  | 470                      | 2.8                   | 9.0                    | 6.0       | —         | 67      | —        | 2.9                   | 90                      | 25 |
| 4       | 18.3       | 1330                        | 710                  | 620                      | 2.1                   | 10.6                   | 4.2       | 0         | 40      | 0        | 1.7                   | 75                      | 34 |
|         |            | 1700                        | 690                  | 1010                     | 1.7                   | 16.6                   | 6.7       | 0         | 40      | 0        | 1.7                   | 65                      | 36 |
| 5       | 12.0       | 890                         | 370                  | 520                      | 1.7                   | 13.6                   | 6.9       | 0         | 51      | 0        | 2.0                   | 105                     | 30 |
| 6       | 19.5       | 1530                        | 790                  | 740                      | 2.1                   | 16.5                   | 9.2       | —         | 56      | —        | 2.2                   | 50                      | 40 |
|         |            | 1500                        | 670                  | 830                      | 1.8                   | 12.9                   | 6.2       | —         | 48      | —        | 1.8                   | 55                      | 45 |
| 7       | 18.4       | 1440                        | 410                  | 1040                     | 1.4                   | 18.7                   | 8.1       | 1.2       | 44      | 6        | 1.6                   | 50                      | 32 |
|         |            | 1620                        | 720                  | 900                      | 1.8                   | 15.4                   | 8.6       | 0.4       | 56      | 3        | 2.1                   | 55                      | 30 |
|         |            | 1670                        | 1080                 | 590                      | 2.9                   | 15.8                   | 11.0      | —         | 69      | —        | 3.1                   | 73                      | 60 |
|         |            | 1850                        | 1440                 | 410                      | 4.6                   | 17.0                   | 12.8      | —         | 76      | —        | 4.0                   | 95                      | 47 |
|         |            | 1620                        | 1080                 | 540                      | 2.7                   | 20.6                   | 12.9      | —         | 63      | —        | 2.6                   | 110                     | 60 |
| 8       | 25.3       | 1110                        | 810                  | 290                      | 4.0                   | 16.0                   | 12.3      | 1.0       | 77      | 6        | 4.3                   | 85                      | 56 |
|         |            | 1300                        | 780                  | 520                      | 2.5                   | 15.4                   | 9.6       | —         | 62      | —        | 2.6                   | 90                      | 45 |
| 10      | 11.5       | 910                         | 690                  | 220                      | 4.2                   | 8.8                    | 7.0       | 0         | 80      | 0        | 4.8                   | 85                      | 42 |
| 11      | 20.2       | 1380                        | 630                  | 750                      | 1.8                   | 9.5                    | 4.1       | 0.1       | 44      | 1        | 1.8                   | 75                      | 50 |
|         |            | 1060                        | 340                  | 720                      | 1.5                   | 11.1                   | 3.9       | 0.3       | 35      | 3        | 1.5                   | 55                      | 48 |
|         |            | 1250                        | 430                  | 820                      | 1.5                   | 11.0                   | 4.4       | 0         | 40      | 0        | 1.6                   | 55                      | 46 |
|         |            | 1580                        | 790                  | 790                      | 2.0                   | 14.3                   | 7.7       | 0.3       | 54      | 2        | 2.1                   | 70                      | 51 |

\*FA, PA, and RA refer to femoral arterial, pulmonary arterial, and right atrial samples respectively.

†When a right atrial nitrous oxide sample was not obtained, an assumed value of 3 per cent was employed in calculating the flow ratio. This value represents the average of the control tests that were obtained under similar conditions.

in table 1. The magnitude of each shunt was expressed as the ratio of pulmonary to systemic flow. This ratio was obtained by relating the systemic arteriovenous difference in nitrous oxide concentration to the pulmonary arteriovenous difference,\* or  $\frac{C_{a_{N_2O}} - C_{r_{N_2O}}}{C_{a_{N_2O}} - C_{p_{a_{N_2O}}}}$ . Since all nitrous oxide concentrations are expressed as a per cent of the arterial concentration, ( $C_{a_{N_2O}} = 100$  per cent), the formula becomes  $\frac{\text{Pulm. flow}}{\text{Syst. flow}} = \frac{100\% - RA\%}{100\% - PA\%}$ . The

\* $C_{a_{N_2O}}$ ,  $C_{r_{N_2O}}$  and  $C_{p_{a_{N_2O}}}$  = concentrations of  $N_2O$  in systemic arterial, right atrial, and pulmonary arterial blood. The derivation of this formula is presented elsewhere.<sup>6</sup>

metered ratios ranged from 1.4 to 4.6 and averaged 2.4.

The pulmonary: systemic flow ratios determined from metered flows are compared to the corresponding ratios derived from the nitrous oxide tests in figure 3. There is no systematic difference between the flow ratios determined by the 2 methods. The coefficient of correlation for these data is 0.96.

When the shunt was closed, mean pulmonary arterial pressures were elevated 5 to 20 mm. Hg above normal. Upon opening of the shunt, mean pulmonary arterial pressure uniformly rose and mean systemic pressure fell. The pressures recorded during each period

of sampling and flow measurement are included in table 1.

### DISCUSSION

The introduction of a plastic loop having a capacity of approximately 100 ml. into the pulmonary circulation resulted in a mild increase in pulmonary arterial pressure. This pressure was further elevated by occlusion of the right pulmonary artery and diversion of the entire pulmonary flow through the loop and the left lung. Under these conditions, a left-to-right shunt was not always well tolerated. Systemic pressure fell and pulmonary arterial pressure rose even further, thus reducing the systemic-pulmonary arterial gradient and limiting the magnitude of the shunt. The right ventricle usually became dilated and the output of both ventricles fell. However, although the output was low, it was possible to maintain a steady flow during which nitrous oxide tests could be performed. In order to relieve the load on the heart, the shunt was closed and the right pulmonary artery opened between sampling periods. Care had to be taken in inserting the cannula into the proximal left pulmonary artery, so that it did not extend too far into the main pulmonary artery and occlude the right.

Frequently, shunts that produced pulmonary to systemic flow ratios in excess of 3:1 were poorly tolerated. Several tests were discarded from the series because they were performed while the flows were falling during the sampling period and their results served only to emphasize the importance of a stable preparation during the sampling. Under these unstable conditions, the magnitude of the shunt was grossly overestimated by the nitrous oxide.

The excellent correlation between metered flows and calculations based upon the nitrous oxide test (fig. 3) establishes the reliability of the inert gas technic for the estimation of the magnitude of a left-to-right shunt. It should be pointed out, however, that only occasionally was it possible to obtain reliable data with shunts producing pulmonary flows in excess of 3 times systemic flow. With these larger

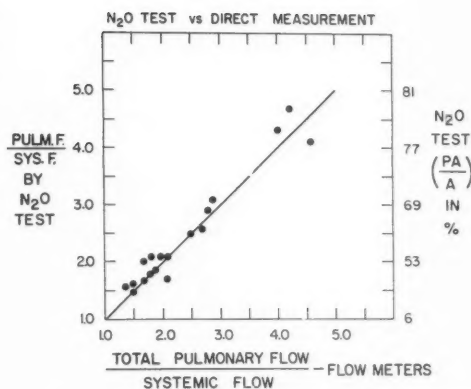


FIG. 3. Pulmonary to systemic flow ratios determined from the nitrous oxide tests compared with those obtained from directly metered flows. The 2 ordinates relate the results of a nitrous oxide test to a given pulmonary:systemic flow ratio.<sup>6</sup>

shunts, the effects of analytic errors became more important with both the direct and indirect techniques, and the correlation between them became correspondingly poorer.

The limitations of the oxygen method for determining the magnitude of a shunt are well recognized. These are the difficulties in obtaining representative samples of mixed venous blood from the venae cavae; a small pulmonary arteriovenous difference; and the normal variations in oxygen content that occur with changes in the metabolic state. With the nitrous oxide test, these shortcomings are minimized. Vena caval samples, proximal to a shunt, are not necessary because the normal nitrous oxide concentration of systemic venous blood is always close to zero during the first 30 seconds of inhalation. In a group of 150 tests carried out in patients, the normal venous content ranged from 0 to 15 per cent of the arterial content and averaged 6 per cent.<sup>6</sup> In the present study, the average systemic venous content was 3 per cent. In the practical applications of the test, it has been found that the average value may be used in calculating the magnitude of shunt without significantly altering the results.<sup>6</sup> In the nitrous oxide test, samples are not drawn while the pulmonary and systemic arterial levels of the gas are constant but during a

time when both are rising. The use of integrated samples drawn simultaneously during most of the period of inhalation minimizes this source of error.

The present study supports the conclusion drawn from extensive clinical application that the nitrous oxide test provides a reliable method for the quantification of a left-to-right shunt as well as for its identification and localization.

#### SUMMARY

Total pulmonary blood flow and blood flow through an artificial left-to-right shunt were measured directly in the dog by means of electromagnetic flowmeters in an extracorporeal extension of the pulmonary circulation. Nitrous oxide tests were then performed while shunts of various magnitudes were functioning. The ratios of pulmonary to systemic flow determined by the nitrous oxide tests correlated well with the ratio obtained from the metered flow measurements, and confirmed the validity of the nitrous oxide technique for the estimation of the magnitude of a left-to-right shunt.

#### SUMMARIO IN INTERLINGUA

Le total fluxo pulmonar de sanguine e le fluxo de sanguine in un derivation artificial sinistro-dextere in un can esseva mesurate directemente per medio de fluxometros electromagnetic in un extension extracorporee del circulation pulmonar. Tests a oxydo nitrose esseva alore affectuate durante que derivationes de varie magnitudes esseva in function. Le proportion inter fluxo pulmonar e fluxo systemic esseva determinate per medio del test a oxydo nitrose e se provava ben correlationate con le proportion obtenite per mesura-

tion directe del fluxo. Le resultado del studio es un confirmation del validitate del technica a oxydo nitrose in le estimation del magnitudine de derivationes sinistro-dextere.

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# Design of a Clinical Ultra-Low Frequency Ballistocardiograph

By ROBERT R. DONALDSON, B.S., DON M. CUNNINGHAM, M.S.,  
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The potential advantages of an ultra-low frequency ballistocardiograph are presented.

**W**HILE the first record of body movement was made over 75 years ago,<sup>1</sup> nearly all of the advances in the field of ballistocardiography have taken place since the entrance of Starr and associates in 1939.<sup>2</sup> During the latter period, several recording techniques have been developed and numerous papers published. However, only within the past 5 years have basic theoretical investigations been made of the dynamic properties of the various ballistic systems by Von Wittern, Burger, Talbot, and Harrison.<sup>3-5</sup> These investigations indicate that the more widely used high frequency and direct body techniques introduce a large degree of distortion into the wave forms and that the more rarely used ultra-low frequency system is the most acceptable of the presently existent methods from this viewpoint. Since comparatively little work has been done with this type of instrument and since it is potentially the most informative, it would seem desirable to acquire more clinical data with the ultra-low frequency instrument. It is the purpose of this paper to describe an ultra-low frequency ballistocardiograph designed for clinical use.

## METHOD

The final device shown in figure 1 evolved from an earlier research instrument shown in figure 2. This conical pendulum suspension of the earlier research instrument can be seen to be that first used by Henderson, and later by Rappaport,<sup>6</sup> employing horizontal rods to offset the support-

ing wires from the vertical. This arrangement performs a dual function, limiting motion to the longitudinal axis of the body, and permitting attainment of ultra-low natural frequencies without the use of excessively long wires.

The suspension of the clinical instrument is shown schematically in figure 3, and is an inversion of the above suspension. The platform is supported by 7 rods, pivoted at both ends, and the angular displacement of the rods from the vertical is maintained by short sections of woven cable. The rods are made from aluminum tubing, with conical hardened steel tips (fig. 5). The tips have been ground and lapped into their individual sockets and are lubricated with a light grease to which a small percentage of stearic acid has been added to reduce friction and wear. The original woven cables have been replaced with strips of steel shim stock,  $\frac{1}{2}$  inch wide and 0.003 inch thick, to reduce the bending stiffness that tends to raise the natural frequency of the platform when the subject is of low weight.

In principle, the operation of this suspension, in either normal or inverted configuration, is analogous to that of an ordinary door swung on frictionless hinges (fig. 4). If the upper door hinge is moved outward slightly, the door will have a definite resting position about which it will oscillate if displaced. The natural frequency of oscillation is a function of the angle  $\theta$  between the hinge axis and the vertical. Since the natural frequency goes to zero  $\theta$  (i.e., the tendency toward oscillation disappears when the hinges are vertically aligned), it follows that the natural frequency can be adjusted to a suitably low value by correct choice of the relative hinge positions. The addition of several wires and rods in the suspension of the instruments shown does not invalidate the analogy, providing all are respectively parallel. The only added complication is several separate but parallel hinge axes, necessitating pivots at the platform, since all points no longer rotate about the same center. Reeves and associates<sup>7</sup> designed a suspension that uses single upper and lower hinge points, removing the necessity for pivots at the platform. (Readers familiar with the concept of virtual dis-

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Supported by the U.S. Public Health Research Grant (H-2151) and by the Maybelle M. Dant equipment fund of the Oregon Heart Association.

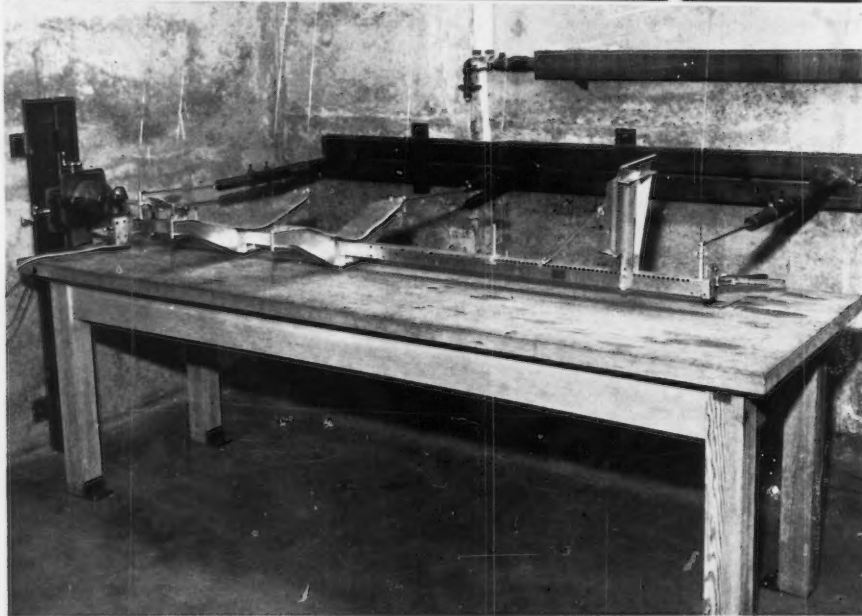


FIG. 1 *Top*. Clinical ballistocardiograph. Headrest and footboard are adjustable; footboard can be clamped to platform to permit application of foot pressure. Honeycomb panel platform is shown locked in position by taggle clamps at each end.

FIG. 2 *Bottom*. Research ballistocardiograph. Suspension similar to that of Rappaport; total weight approximately  $8\frac{1}{2}$  pounds. Loud-speaker motor for application of external force to body can be seen at left-hand side of photograph.

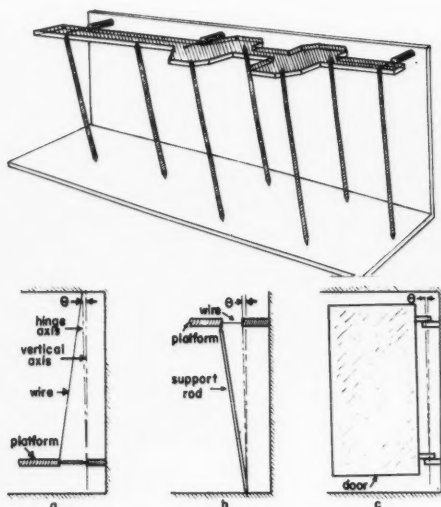


FIG. 3 Top. Diagram of suspension of clinical instrument. Platform is supported on 7 rods, pivoted at each end, and is held in lateral position by 3 flexible cables.

FIG. 4 Bottom. Diagram of A, Rappaport's suspension, B, inversion used in clinical instrument, C, analogous door suspension.

placements may notice that these suspension systems cause any point on the platform to trace a portion of a rim of a cone during platform motion and that a vertical cone axis will therefore result in no change of potential energy of the platform upon a virtual displacement, which is the criterion for aperiodicity.)

The natural frequency of this type of suspension is independent of platform load, except for the slight effect of the lateral resistance to deflection of the thin steel strips used to maintain the offset platform position. The natural frequency of platform oscillation is 0.16 c.p.s. with a 75-pound load; increasing the load to 200 pounds reduces the natural frequency to 0.11 c.p.s. This characteristic provides adequate reduction of respiratory interference and convenience of instrument use for a large range of patient weights. Platform friction damping also varies somewhat with load; values fall in the range of 5 to 10 per cent of critical equivalent viscous damping for loads between 75 to 200 pounds.

In order to raise the natural frequency of relative motion between body and platform (von Wittern's  $F_2$  frequency<sup>2</sup>), platform weight should be minimized. Practical experience also indicates that a platform providing rigid vertical support for the body is desirable, although this has never

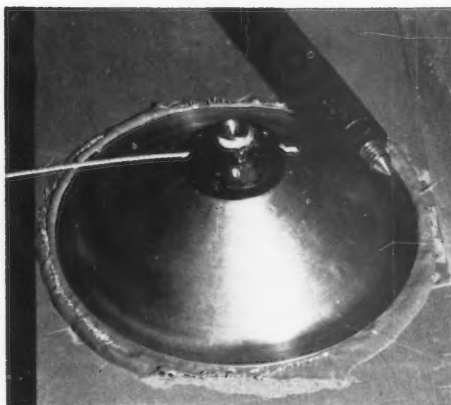


FIG. 5. Detail of platform support. Aluminum cone is bonded to underside of platform, providing for cable attachment; pointed tip of rod fits into small conical socket.

been conclusively demonstrated. To provide both low weight and rigidity, a "sandwich" structure was chosen for the platform, because of an inherently high ratio of stiffness to weight. The outer supporting sheets are of high strength aluminum alloy, 0.012 inch thick, and are bonded to a "honeycomb" cellular aluminum core. The core is 1 inch thick and the hexagonal cells are of  $\frac{1}{4}$  inch width, with 0.001-inch wall thickness.<sup>3</sup> Cones spun from 0.020-inch aluminum sheet are bonded to the underside with an epoxy resin, to permit attachment of the horizontal strips and pointed support rods (fig. 5). As seen in figure 1, an irregular platform shape was utilized to reduce weight further, while providing adequate support for a range of body sizes. The total weight of the platform, including headrest, footboard, and transducers, is 6.86 pounds. Removable elbow rests (not shown) are necessary for some patients, and increase the weight to 7.0 pounds.

The frame of the instrument is of welded steel construction with a total weight of approximately 500 pounds. A plywood panel is located beneath the platform, containing circular holes to permit passage of the support rods. Quick-acting clamps are located at either end to lock the platform in position, and a handwheel, connected to a nut-and-screw assembly, permits adjustment of the null position of the platform by causing slight lateral movement of the fixed ends of the horizontal steel strips. Leveling screws are located at the four corners, and the frame is supported

\*Available from the Dumont Corporation, San Rafael, Calif.

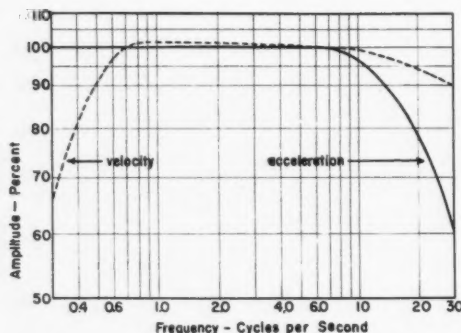


Fig. 6. Frequency response curves. Curves are for entire recording systems, from transducer input to recorder pen output.

on four  $\frac{1}{2}$ -inch thick, hard rubber pads to reduce background vibration. Building vibration was still found to be a problem, and it was necessary to locate the instrument in a basement room.

The clinical instrument is equipped to measure displacement, velocity, and acceleration (plus the electrocardiogram), since it is conceivable that any of these might yield significant clinical information; however, since the displacement curve is simple and invariant, and since it has been found to be quite difficult to obtain without extreme baseline weave, recording of displacement has been discontinued.

Acceleration is measured with 2 Schaevitz Model HG5 accelerometers,<sup>\*</sup> which are connected to carrier preamplifier units of a Sanborn 150-100A 4-channel recorder. These accelerometers are a seismic type, and operate on a differential transformer principle. They have a natural frequency of 42 c.p.s. when damped 71 per cent of critical, and a weight of 4 ounces. The over-all amplitude frequency response for the accelerometer-recorder system is shown in figure 6. (No accurate phase shift curves have been obtained.)

One of these accelerometers is mounted on the platform, and the other is securely strapped between the ankles of the patient. The two provide very similar, but not identical, records (fig. 7), thereby providing a check on one another, which is useful in detecting transducer difficulties. Both accelerometers are calibrated to produce a 1 cm. pen deflection for an input of 2 cm. per second.<sup>2</sup> Since the accelerometers respond to a static input, and since a rotation from horizontal to vertical corresponds to an input of one g, or 980 cm. per second,<sup>2</sup> calibration is accomplished with a device which rotates the accelerometers through an angle having a sine of  $2/980$ .

\*Available from Schaevitz Engineering, Camden, N.J.

The velocity of the platform is measured with a bar-magnet and coils,<sup>\*</sup> of the type used by Rappaport.<sup>6</sup> The signal is fed into a Sanborn AC-DC preamplifier, which is operated on alternating current to produce attenuation below 1 c.p.s., thereby reducing baseline weave from respiration. The frequency response curve is also shown in figure 6. The velocity measuring system is calibrated to produce a 1-cm. pen deflection for an input of 0.1 cm. per second calibration being accomplished with a shaking table. Displacement can be obtained by use of a resistance-capacitance integrator circuit placed between the coil output and the AC-DC preamplifier input.

## RESULTS

Two sample records taken with the clinical instrument are shown in figure 7. Both records were taken during respiration under basal conditions. The record on the left was taken on a clinically normal young woman; that on the right was taken on a young man suffering from an atrial septal defect. Both records are consistent from cycle to cycle and resemble those of other workers; comparatively larger amplitude of the high frequency detail appears in the record taken directly from the body. Further discussion of clinical data will be given in a subsequent communication.

## DISCUSSION

The inverted suspension has resulted in several improvements, compared to the formerly used configuration. It has been possible to enclose the instrument in a rigid, compact, and semi-portable unit. The overhead wires are eliminated, removing a hindrance to the patient using the instrument, and in addition, a possible source of spurious vibration. From a structural viewpoint, suspension from below permits optimum placement of the points of support without interference with the body of the patient. Further, a slight psychologic advantage is gained from the more innocuous appearance of the instrument with the suspension concealed beneath the platform. The suspension system requires initial adjustment, but once adjusted it provides trouble-free operation over a long period of time.

\*Available from Sanborn Co., Cambridge, Mass.

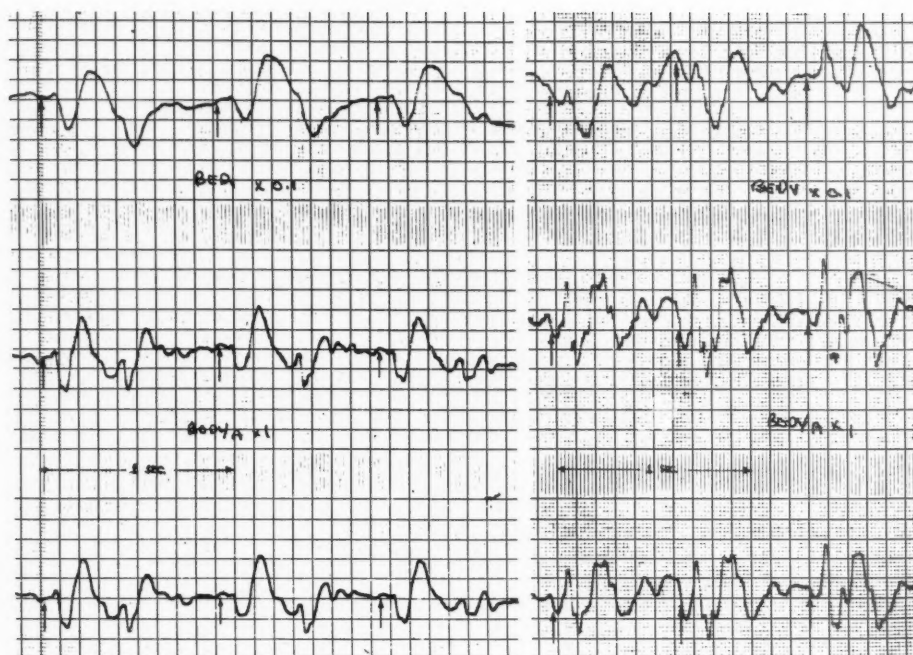


FIG. 7. From top to bottom, platform velocity, body acceleration (at ankles), and platform acceleration. Left side, clinically normal 18-year-old female; right side, 19-year-old male with atrial septal defect. Arrows, S waves of electrocardiogram. Both records were taken during normal respiration and under basal conditions.

The omission of body restraints, to increase coupling between body and platform, is a design decision based on several factors. First, restraints are self-defeating to some extent in that they increase the weight, which must move in unison with the body. Secondly, although the increased coupling may raise the calculated " $F_2$ " frequency, all of the theoretical analyses thus far presented are based on the simplifying assumption that the body behaves as a rigid mass over the entire ballistocardiographic frequency spectrum. Deviation of the actual behavior from the ideal behavior, due to the segmental motion of various parts of the body, may introduce a degree of distortion larger than that caused by body-platform interaction. Unpublished studies have been made in this laboratory (with use of the instrument of figure 2, which has a weight of  $8\frac{1}{2}$  pounds) in which a known external sinusoidal force of variable frequen-

cy was applied to the body,<sup>8</sup> and the acceleration of the platform and of various body points was measured. If the body behaved as a rigid unit, a graph of the product of mass and acceleration divided by force, versus frequency of excitation as an argument, would yield curves similar to those presented by Burger et al.<sup>4</sup> The experimental curves indicate an amplification of about 2 to 4 in the upper half of the frequency spectrum, varying considerably from subject to subject: A variety of restraints were devised and tested in an attempt to reduce the distortion, and it was found that the degree of restraint (i.e., from footboard only to footboard with shoulder clamps, wrist, hip, knee, and ankle straps, plus girdle and cervical brace) had a rather small effect on the higher frequency distortion. The tentative conclusions are (a) that the body-platform interaction causes a comparatively small part of this distortion.

due to the small effect of large variations in body-platform coupling; and (b) that the body tissues are so compliant as to make body restraints ineffective, the tissues simply moving within the restraints, like jello in a rigid bowl. There is need for further investigation in this area in order to determine what phenomena occur within the body at the higher ballistocardiographic frequencies, with a view toward counteraction of the effects (perhaps by electronic means, similar to the method of Schwarzschild<sup>9</sup>).

The last reason for omission of additional restraints is related to the psychological effect on the patient. It is desirable that the patient be fully relaxed during the recording period, in order to obtain a basal heart rate and to eliminate artifacts in the record due to tremor of tensed muscles. For the uninitiated clinical patient, restraints may cause mental apprehension and physical discomfort to the extent of preventing complete relaxation.

In view of the amplification caused by the body, the high-frequency attenuation of the accelerometers may be desirable, although it was not found to be sufficient to compensate fully for the body amplification. It is considered that, for the present, the high-frequency components of the ballistocardiogram should be treated with reserve until more information is available regarding the body dynamics in this frequency range. Some interesting and encouraging progress has been made by Reeves and associates in the correlation of high-frequency detail in ultra-low frequency records with physiologic events,<sup>10</sup> but it still cannot be determined whether an abnormality in high-frequency detail is a reflection of cardiovascular irregularity, or whether it is due to a variation in the physical properties of the body of the subject.

#### SUMMARY

The design and construction of an ultra-low frequency ballistocardiogram for clinical use has been presented. Technical data regarding the suspension, platform, and transducers are included, following the recom-

mendations of the "Committee on Ballistocardiographic Terminology." Some discussion of factors influencing particular design choices have been given. Sample records of a normal and an abnormal subject are contained in the illustrations.

#### ACKNOWLEDGMENT

The authors would like to express their appreciation to Mr. Tom Kornell of the Boeing Aircraft Company for his suggestions in the design of this instrument.

#### SUMMARIO IN INTERLINGUA

Le plano e le construction de un ballistocardiographo a frequentia ultra-basse pro uso clinic es describite. Es includite datos technic relative al suspension, platteforma, e transductores, secundo le recommendationes del "Committee pro le Terminologia Ballistocardiographic." Ee presente un breve analse de certe factores que determina le selection del un o del altere typo de construction pro ballistocardiographos. Specimens de registrationes obtenite ab subjectos normal e anormal es continite in le illustrationes.

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Winters, W., Wilson, M., Chungcharoen, D., Stauffer, H. M., Durant, T. M., and Oppenheimer, M. J.: Use of Intravascular Carbon Dioxide Gas to Demonstrate Interatrial Septal Defects. *Am. J. Physiol.* **195**: 579 (Dec.), 1958.

It has been demonstrated that carbon dioxide gas can be safely used to visualize the right side of the heart with little or no disturbances in hemodynamics. The gas has also been used with no untoward effects on the left side in normal dogs. The present study was to determine the usefulness of carbon dioxide gas in demonstrating interatrial septal defect in the dog. A cinefluorographic technic gave a permanent record of the course of injected carbon dioxide gas and physiologic measurements were made at the same time. Gas injected into the right heart was detected shortly afterward in the left atrium and then as a residual bubble in the left ventricle for 10 to 15 seconds. Gas passed rapidly from the right to the left atrium, despite the fact that the shunts were mainly from left to right. Pressures recordings in the right atrium indicated that values above 100 mm. Hg could be record for 1 to 5 seconds after introduction of gas, but little change in pressure readings was noted in the left atrium. At the time the gas passed through the defect the systemic pressure rose; if no defect was present the systemic pressure fell. Radiologic detection of gas in the left atrium and then in the left ventricle and motion picture recordings suggest that it will be possible to estimate both the size and position of the defect by duration, shape, and position of the gas bubble. The dissolution of the residual bubble is an important problem.

KAYDEN

## Right Atrial Myxoma

By MARTIN S. BELLE, M.D.

**A**TRIAL myxomas can be successfully removed.<sup>1-5</sup> Apparently left atrial myxomas are infrequent and those in the right atrium are approximately 25 per cent as common.<sup>6</sup> Bahnson and Newman<sup>7</sup> in 1953 reported the first removal of a right atrial myxoma and since that time 4 others have been operated upon. Ripstein<sup>8</sup> in 1953 attempted unsuccessfully to remove a right atrial myxoma through the open right atrium under hypothermia; this tumor extended through the septum into the left atrium.

Recently Coates and Drake<sup>5</sup> reported the successful removal of a right atrial myxoma under open-heart conditions. This patient had a variable right-to-left shunt through a patent foramen ovale. Lyons and his group<sup>9</sup> were unsuccessful in removal of a similar tumor under open-heart surgery. They thought that death was due to a flabby myocardium and the production of total tricuspid insufficiency upon removal of the myxoma, which had previously caused tricuspid stenosis.

Since myxomas of the atria can be successfully removed, it is important to diagnose the lesion correctly so that an otherwise fatal condition may be corrected and the patient restored to health.

### CASE REPORT

A 43-year-old white woman gave a history of long-standing nervousness and unexplained infertility. Her diet had been poor in proteins and high in alcohol.

Her childhood history was negative for any stigmata of rheumatic fever but she was first thought to have a heart condition when she first entered school and was restrained from strenuous activities. Nevertheless, she pursued all normal activities and had no reason to see a physician for approximately 35 years.

In April 1955 she developed a swelling of her feet and ankles after acute emotional stress. An

enlarged liver and a murmur of the heart were found, and she was told that she had heart failure. After several days of bed rest the edema cleared without drugs.

In July 1955 right heart catheterization was done by Dr. Frank Hernandez of the National Children's Cardiac Home. An intracavitary electrode was used to permit accurate localization of the catheter. A high right atrial pressure was found with a diastolic gradient between the right atrium and ventricle (fig. 1 and table 1). Pulmonary artery and capillary pressure were not elevated even after exercise. The right atrial pressure curve showed no evidence of tricuspid insufficiency. No definite evidence of a left-to-right shunt was found. A slight to moderate degree of oxygen unsaturation of the brachial artery was present which was thought to be due to lung disease or a patent foramen ovale with a right-to-left shunt. Because the oxygen saturation increased on exercise, chronic lung disease was thought more likely to be the cause of the oxygen unsaturation. A diagnosis of tricuspid stenosis was made and the patient sent to an eastern medical center for surgery. There, after careful clinical evaluation, a diagnosis of Ebstein's anomaly was made and she was advised not to have surgery.

When first seen by us on January 31, 1956, the patient appeared nervous, hyperactive, and chronically ill. She complained of extreme weakness and pain in both shoulders. The blood pressure was 90/72, and the pulse was 79 and regular. Cyanosis or clubbing was not evident. The neck veins were hyperactive but not distended and a prominent pulsation was present which was synchronous with a very loud presystolic murmur heard along the left sternal border. No chest deformity was present. A pulsation was noted over a small area to the left of the sternum in the third and fourth intercostal spaces which preceded the apex impulse. The heart was not enlarged to the left, but the right border of dullness extended 3 cm. to the right of the sternum in the third and fourth intercostal spaces.

Auscultation revealed increased and split S, but no systolic murmur. A loud presystolic murmur was heard along the left sternal border followed by a third heart sound. At the base there were no murmurs, and both aortic and pulmonary second sounds were diminished. Upon inspiration and with the Valsalva maneuver the presystolic murmur over the xiphisternal area increased. Positional changes had no effect on the murmur.

From the Department of Cardiology, Jackson Memorial Hospital, Mercy Hospital, and the University of Miami Medical School, Miami, Fla.

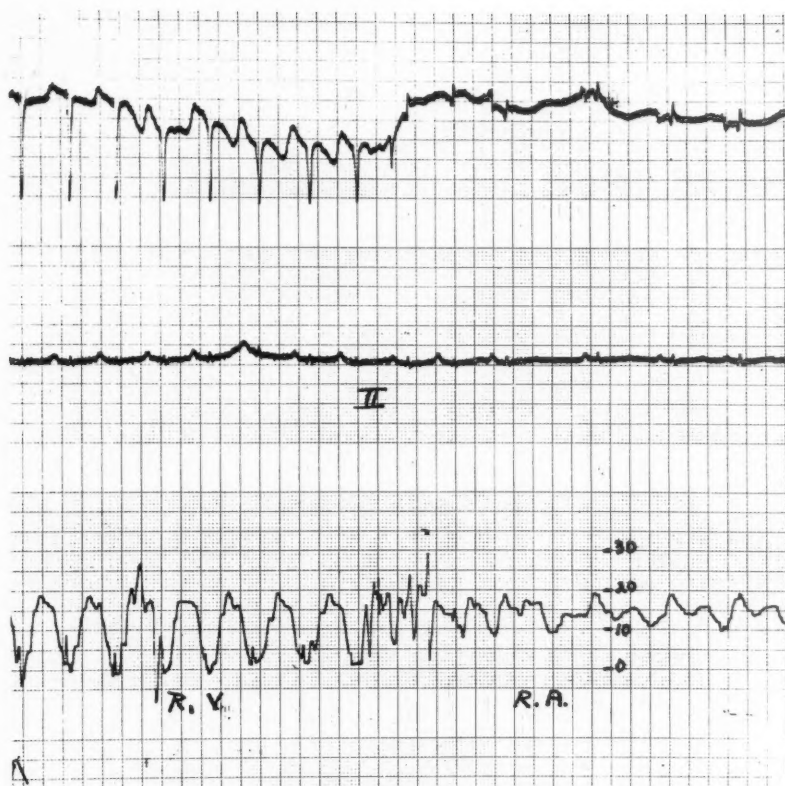


Fig. 1 *Top*, intraecavitary electrocardiograph; *middle*, lead II of the electrocardiograph; and *bottom*, pressure tracings of right ventricle and right atrium. The intraecavitary electrode rules out the possibility of Ebstein's anomaly, since there is a ventricular type of QRS complex with the ventricular pressure curve and atrial type of QRS complex with the atrial pressure curve. The atrial pressure curve shows its lowest point before atrial contraction, which is not characteristic of curves with tricuspid stenosis and should suggest another cause for the atrioventricular diastolic pressure gradient.

The lungs were clear and resonant throughout. The liver was felt 2 fingerbreadths below the costal margin with a smooth, nontender edge. There was no ascites or edema.

Blood counts, urinalysis, and serum proteins were normal. The cephalin flocculation test was 1+ and there was 13 per cent retention of bromsulphalein in 45 minutes.

X-ray of the chest (fig. 2) showed a globular cardiac silhouette with suggestive slight generalized enlargement and right atrial enlargement. The pulmonary artery and pulmonary vascularity were diminished. Slight shelving of the right ventricular outflow tract was present, suggesting right ventricular enlargement. Fluoroscopy confirmed these findings and showed no abnormal pulsation in any chamber.

The electrocardiogram (fig. 3) showed low voltage throughout, clockwise rotation, very low potential over the right precordial leads, and relatively prominent P waves. It suggested right atrial hypertrophy and very little right ventricular musculature.

Ventilatory studies showed marked restriction of the maximum breathing capacity and a fairly normal vital capacity.

On February 26, 1956, the patient had a sudden attack of fainting; 30 minutes later she was still semi-stuporous, but conscious and slightly cyanotic. There was no change in the cardiac findings except an irregular sinus rhythm that varied between 80 and 120 beats per minute (fig. 4). Within an hour from the original episode she was completely oriented.

TABLE 1.—Catheterization Data Showing a Small But Definite Diastolic Pressure Gradient between Right Atrium and Ventricle. The Cardiac Output Is Also Considerably Reduced

| Catheter position      | Oxygen         |                                | Pressure     |               |             |
|------------------------|----------------|--------------------------------|--------------|---------------|-------------|
|                        | Content vol. % | Saturation %                   | Syst. Hg mm. | Diast. Hg mm. | Mean mm. Hg |
| At rest                |                |                                |              |               |             |
| Superior vena cava     | 6.8            | 44.5                           | 11           | 6             | 8           |
| Inferior vena cava     | 8.3            | 54.3                           | 15           | 11            | 14          |
| Right atrium—high      | 7.0            | 45.8                           | 13           | 5             | 9           |
| low                    | 8.3            | 54.3                           | 12           | 7             | 10          |
| Right ventricle—mid    | 7.0            | 45.8                           | 17           | 3             | 7           |
| Main pulmonary artery  | 7.5            | 49.2                           | 17           | 7             | 10          |
| Right pulmonary artery | 7.52           | 49.2                           | 15           | 8             | 11          |
| Pulmonary capillary    |                |                                |              |               | 5           |
| Brachial artery        | 13.28          | 86.6                           | 105          | 63            |             |
| Exercise               |                |                                |              |               |             |
| Right atrium           |                |                                | 18           | 6             | 12          |
| Right ventricle        |                |                                | 28           | 4             | 15          |
| Right pulmonary artery | 6.52           | 41.1                           | 13           | 8             | 13          |
| Brachial artery        | 14.3           | 90.5                           | 120          | 68            |             |
|                        | Flow ml./min.  | Index ml./min./M. <sup>2</sup> |              |               |             |
| At rest                | 2610           | 1900                           |              |               |             |
| Exercise               | 3900           | 2850                           |              |               |             |

Since we thought that the catheter studies with the intracavitary electrode were against the diagnosis of Ebstein's anomaly,<sup>20, 21</sup> angiocardigraphic studies were done on March 2, 1956.

The angiocardigram (fig. 5) showed an irregular filling defect approximately 7.5 by 6 cm.; it was interpreted as being a myxoma attached to the right atrial septum which prolapsed through the tricuspid valve and produced tricuspid stenosis with obstruction of the inflow tract of the right ventricle.

Surgery was undertaken with hypothermia and the patient was cooled to 31 C. The inflow tract was occluded for about 4 minutes. The tumor (fig. 6) was a polypoid pedunculated mass growing from the lower portion of the interatrial septum and obviously obstructing the inflow of blood to the right ventricle. No interatrial septal defect was present. The patient's immediate post-operative condition was good. She responded somewhat about 6 hours after surgery with a few



FIG. 2. X-ray of the chest shows globular-shaped heart with slight generalized enlargement and suggestive right atrial enlargement.

words but there was no motion of the right side of the body and impaired motion on the left. Her condition gradually deteriorated, shock supervened, and the heart failed. Death occurred approximately 24 hours after surgery.

The pathologic report (fig. 7) of the tumor was consistent with myxoma.

#### DISCUSSION

Of course the prime unequivocal diagnostic tool for atrial myxoma is angiocardigraphy. This must be done in any case in which a tumor is suggested prior to surgical intervention. However, with the experience in this case and a review of the other right atrial myxomas certain important clinical and physiologic findings may help in deciding when to do angiocardigraphy. Harvey<sup>12</sup> wrote an excellent review of the findings in left atrial myxomas but we think that right atrial myxomas present a few different diagnostic aspects which should be emphasized.

Table 2 summarizes the findings in the reported cases of right atrial myxoma. The presenting symptoms in 3 of the 7 patients was right-sided failure and eventually this was present in a fourth patient. Two patients simulated the historical findings in subacute bacterial endocarditis. One was asymptomatic.

The heart may or may not be enlarged. The enlargement may be both right and left-sided or may be right ventricular and atrial

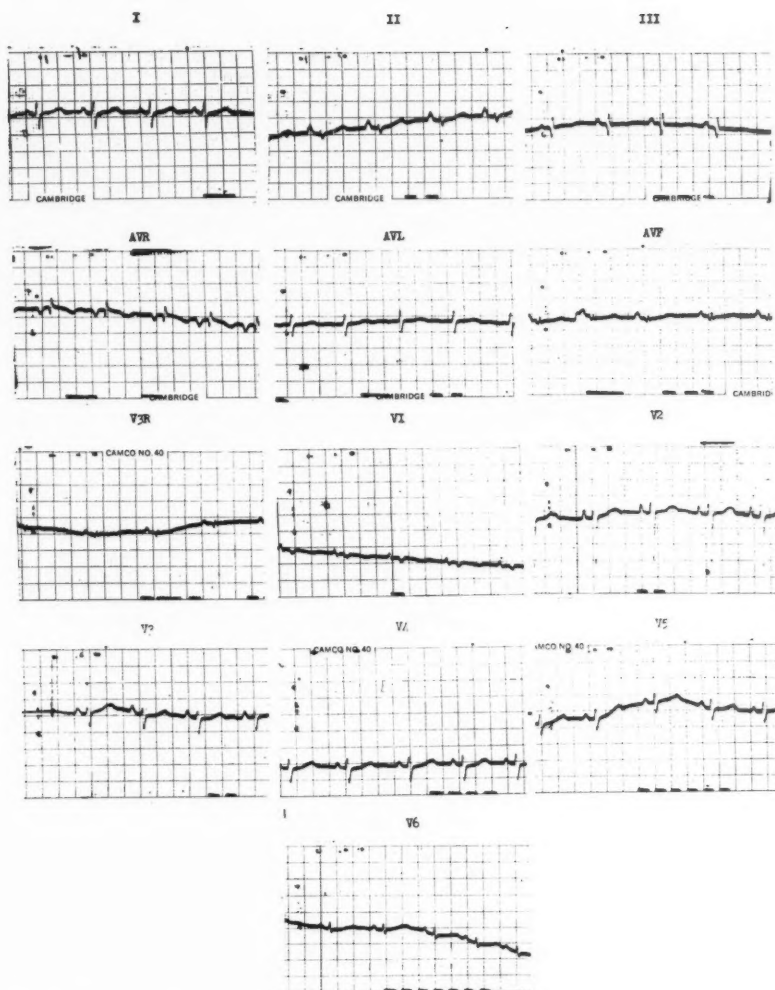


FIG. 3. Electrocardiogram showing low voltage throughout, clockwise rotation, low potential over right precordial leads, and relatively prominent P waves. (This tracing and the one from the patient of Coates and Drake<sup>5</sup> could practically be superimposed.) (Also seen in Ebstein's anomaly.)

only. One patient<sup>13</sup> had intracardiac calcification on the right side. The electrocardiogram presented findings of prominent P waves in the limb leads and right precordium in 3 cases with low voltage of QRS over the right precordium. This is not unlike the electrocardiogram seen in Ebstein's anomaly.<sup>14, 15</sup> Atrial fibrillation may be present.

In our case when the patient had an attack

of syncope, the heart rate on the electrocardiogram varied between 72 and 120 (fig. 4) without relation to respiration or change in rhythm, and with no apparent physiologic reason. This fact may suggest intermittent obstruction to flow.

Catheterization may help in deciding that something other than valvular disease is present.

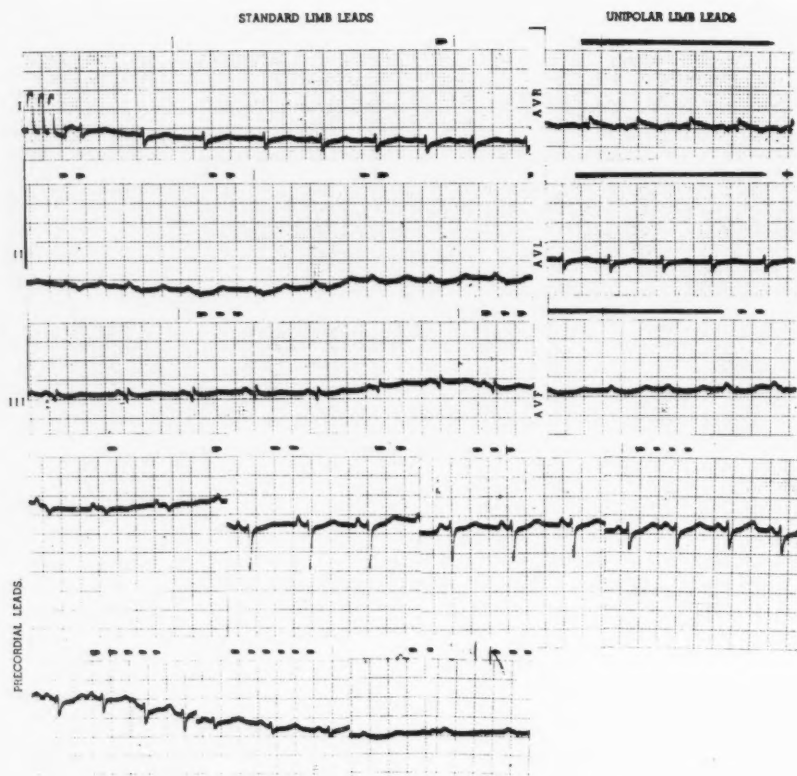


FIG. 4. Electrocardiograph taken at time of an attack of syncope and semi-coma which lasted about 30 minutes. Note marked variation in rate without change in rhythm, which may be a hint of intermittent obstruction. In  $V_5$  the rate is approximately 125 to 140, while in lead 3 the rate is 70 to 100.

In 2 cases, our own and that of Coates and Drake,<sup>5</sup> a diagnosis of Ebstein's anomaly was made prior to angiocardiography. Coates and Drake<sup>5</sup> could not clearly define the atrioventricular junction. In our case an intracavitary electrode catheter was used, which obviated this difficulty. As shown by Hernandez and co-workers<sup>10</sup> and Yim et al.<sup>11</sup> the diagnosis of Ebstein's anomaly can be made with a greater degree of certainty with the use of an intracavitary electrode catheter along with the pressure curves. Also, as Bahnson (fig. 8) pointed out, the atrial pressure curve may suggest that something other than tricuspid stenosis is present. The atrial curve that he secured showed that the lowest point of pres-

sure occurred just before ventricular contraction, which suggested to him that intermittent obstruction was present.

Two cases showed atrial curves consistent with tricuspid stenosis and insufficiency without symptoms. This alone should lead one to suspect other than valvular disease in spite of an adequate right atrioventricular diastolic gradient.

The atrial pressure (fig. 1) curve in our case also showed its lowest point of pressure in diastole just before atrial contraction, at which time with tricuspid valvular stenosis atrial pressure should be rising rather than decreasing. This should make it imperative that angiocardiography be done.

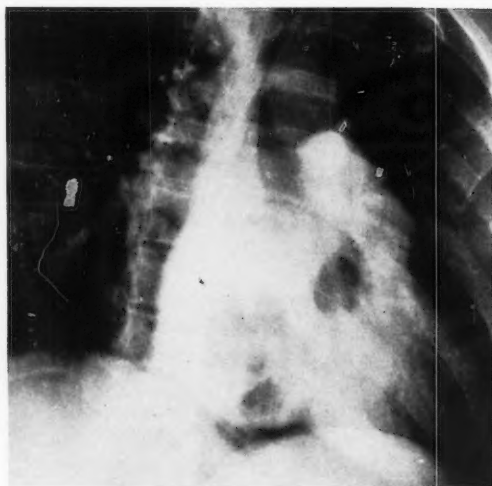


FIG. 5 *Left*. Angiocardiogram showing tumor of the right atrium with prolapse into the right ventricle.



FIG. 6 *Right*. Photograph of polypoid myxoma which was attached to the lower portion of the interatrial septum on the right.

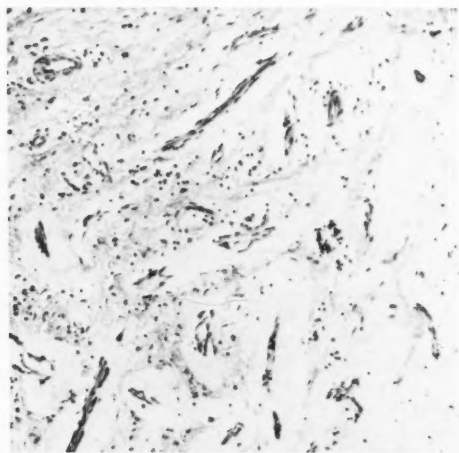


FIG. 7. Microscopic photograph of myxoma showing irregular and varied-size masses of amorphous, cellular, and slightly granular material.

Finally, if surgical intervention is contemplated open-heart operation with a pump oxygenator and artificially stopped heart seems to be the method of choice. To date, to our knowledge, this method was used in the only successful operation for a right atrial myxoma with long-term survival.

#### SUMMARY

A case of myxoma of the right atrium with physiologic, surgical, and angiocardiographic findings has been presented together with a review of 6 other published cases.

Several findings have been emphasized that may call attention to the possible diagnosis of right atrial myxoma: right-sided heart failure; intracardiac calcification of the right heart; enlargement of the right ventricle and right atrium; electrocardiographic findings of a prominent P wave and low voltage over right precordium simulating that found in Ebstein's anomaly and marked variation in heart rate not related to any physiologic event or change in rhythm; use of intracavitary electrode catheter to rule out Ebstein's anomaly; and finally, analysis of the right atrial curve may lead one to suspect that other than valvular stenosis is present.

Angiocardiography gives a definitive diagnosis.

Cure may now be obtained with surgical removal of myxomas; therefore, it is important that they be detected during life.

TABLE 2.—*Summary of the Clinical and Physiologic Findings of the Reported Cases of Right Atrial Myxoma*

| Case                   | Presenting symptoms                                      | Auscultatory findings  | X-ray of chest   | Electrocardiogram   | Catheterization findings  | Angiocardiographic findings  |
|------------------------|--|--|--|---|---|--|
| 1. Bahnson and Newman  | Right sided heart failure                                | Short soft systolic murmur and rumbling diastolic murmur along left sternal border | Normal   | —   | Right atrial curve suggestive of intermittent obstruction   | —  |
| 2. Facquet et al.      | Asymptomatic   | —  | Enlarged heart   | —   | —   | Filling defect right atrium and inflow tract right ventricle   |
| 3. Ripstein            | —  | —  | —  | —   | —   | —  |
| 4. Coates and Drake    | Simulated subacute bacterial endocarditis                | Apical and pulmonic systolic murmur with variable 3rd and 4th heart sound          | Right sided cardiac enlargement  | Prominent P with low voltage QRS  | No right atrium right ventricle pressure gradient. No clear cut transition from atrium to ventricle | Lobulated filling defect in right atrium with apparent protrusion through tricuspid valve into right ventricle |
| 5. Lyons et al.        | Right sided heart failure                                | Presystolic murmur loudest at tricuspid area                                       | Enlarged right ventricular contour   | Prominent P in II, III, and V leads with QRS in V <sub>1</sub> and V <sub>2</sub> | Right atrial curve suggested tricuspid stenosis and insufficiency (No clinical signs of latter)     | Large non-opacified mass in right atrium   |
| 6. Bayer von O. et al. | Fever and enlarged heart followed by right sided failure | Systolic murmur over lower sternal area  | Heart enlarged to right and left. Intracardiac calcification right side of heart | Atrial fibrillation   | Atrial curve showed tricuspid stenosis and insufficiency (No clinical signs of latter)              | Right atrium markedly enlarged with roundish irregular filling defect in the region of A-V junction            |
| 7. Belle               | Right sided heart failure                                | Presystolic murmur at left sternal border with variable 3rd heart sound            | Enlarged right atrium and suggestive right ventricular enlargement               | Prominent P with low voltage QRS. Marked variation in rate                        | Right atrial curve showed lowest point in diastole with abrupt rise with atrial contraction         | Filling defect 7.5 x 6 cm right atrium which prolapsed through tricuspid valve into right ventricle            |

## SUMMARIO IN INTERLINGUA

Es presentate un caso de myxoma del atrio dextere, con datos physiologic, chirurgic, e angiocardiographic. Ee etiam presentate un revista de 6 altere casos in le litteratura.

Plure constatactiones es sublineate proque illos suggere de possibile diagnose de myxoma dextero-atrial. Illos es (1) disfallimento cardiac dextero-lateral, (2) calcification intracar-

diale del corde dextere, (3) allargamento del ventriculo dextere e del atrio dextere, (4) in le electrocardiogramma, prominentia del unda P e basse voltage super le precordio dextere, simile al constatactiones in casos del anomalia de Ebstein, e marcate variation del frequentia cardiac, non relationate a ulle evento physiologic o a ulle alteration del rhythmo, (5) le uso del catheter a electrodo intracavitari pro

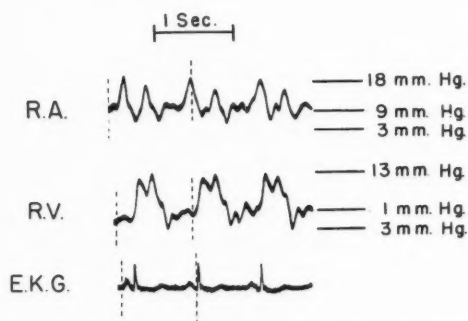


FIG. 8. Pressure tracings of case reported by Bahnson<sup>7</sup> showing elevated atrial pressure with the contour of the curve suggesting a valve mechanism which is released between atrial and ventricular contraction. The lowest point on the atrial curve is just before ventricular contraction. (Courtesy and permission of the authors and Johns Hopkins Press.)

## PRESSURES

|                   | mm. Hg. | mean |
|-------------------|---------|------|
| Pulm. "capillary" |         | 5    |
| Pulm. artery      | 14/5    | 9    |
| R. ventricle      | 18/0/4  | 9    |
| R. auricle        | 18/3/9  | 12   |
|                   | 20/8/12 | 14   |

CARDIAC OUTPUT 1.34 L/M<sup>2</sup>/MIN.

excluser le presentia de anomalia de Ebstein, e (6) le analyse del curva dextero-atrial supporta frequentemente le suspicion que un condition altere que stenosis valvular es presente.

Angiocardiographia produce le definitive diagnose.

Curation es nune effectuable per le abalation chirurgie de myxomas. Ergo, le detection de myxoma dextero-atrial durante le vita del patiente es importante.

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## Use of a Calcium Chelating Agent (NaEDTA) in Cardiac Arrhythmias

By BURTON D. COHEN, M.D., NORTON SPRITZ, M.D., GLENN D. LUBASH, M.D.,  
AND ALBERT L. RUBIN, M.D.

The interrelated effects of digitalis and various cations on cardiac rhythmicity are the subject of much recent interest. This paper presents additional data on this subject that carry important therapeutic implications. The chelating agent, disodium ethylene diamine tetra acetate (NaEDTA), has been used intravenously in 14 instances of supra-ventricular and ventricular arrhythmia. Digitalis had been administered previously in 13 instances, and various degrees of digitalization were encountered. This report summarizes our experience with NaEDTA as a test of the degree of digitalis therapy and as treatment of the arrhythmias observed.

IT HAS been demonstrated that calcium and digitalis act synergistically on both myocardial contractility and irritability.<sup>1-6</sup> Nalbandian et al.<sup>7, 8</sup> have used this relationship practically and have developed an intravenous calcium tolerance test to quantitate the degree of digitalization. With this and other provocative tests, however, the end point may be a fatal arrhythmia.

Calcium binding, on the other hand, can be induced in vivo through the intravenous use of the chelating agent, disodium ethylene diamine tetra acetate (NaEDTA) without significantly altering plasma potassium or magnesium.<sup>9, 10</sup> Experiments in animals<sup>10, 11</sup> and in man<sup>12, 13</sup> have shown that reduction in calcium ion so induced can affect arrhythmias resulting from digitalis therapy. Since reversal of arrhythmia is a positive end point, we have used rapidly injected intravenous NaEDTA\* in patients with arrhythmias, most often in the setting of previous digitalis administration.

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This study was supported in part by the New York Heart Association and the U.S. Public Health Service (H-2054C).

\*Supplied by Murray Weiner, M.D., of Geigy Pharmaceuticals.

### MATERIALS AND METHODS

Thirteen patients with cardiac arrhythmias were chosen for study. All but one had received digitalis. They were treated on 14 occasions with intravenous injections of NaEDTA diluted with 5 per cent dextrose in water to a concentration of 20 mg. per ml., given at rates of 5 to 25 ml. (100 to 500 mg.) per minute. During the procedure a continuous electrocardiogram was taken on a direct-writing machine. One of the standard 12 electrocardiographic leads was employed in most cases. In one patient esophageal leads were obtained and in another a bipolar atrial lead using the second and fourth interspace to the right of the sternum (designated Lewis lead) was

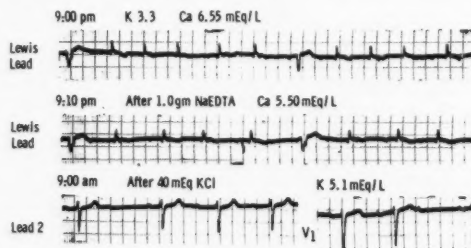


FIG. 1. Electrocardiograms in patient M.M. showing atrial tachycardia with A-V block and ventricular premature contractions (9:00 p.m.). NaEDTA produced no change in the arrhythmia (9:10 p.m.). Following potassium chloride intravenously the electrocardiogram reverted to normal sinus rhythm with Wenckebach phenomenon (leads II and V<sub>1</sub> at 9:00 a.m.). The latter persisted for 16 days and was followed by an episode of nodal rhythm and, finally, normal sinus rhythm without A-V block.

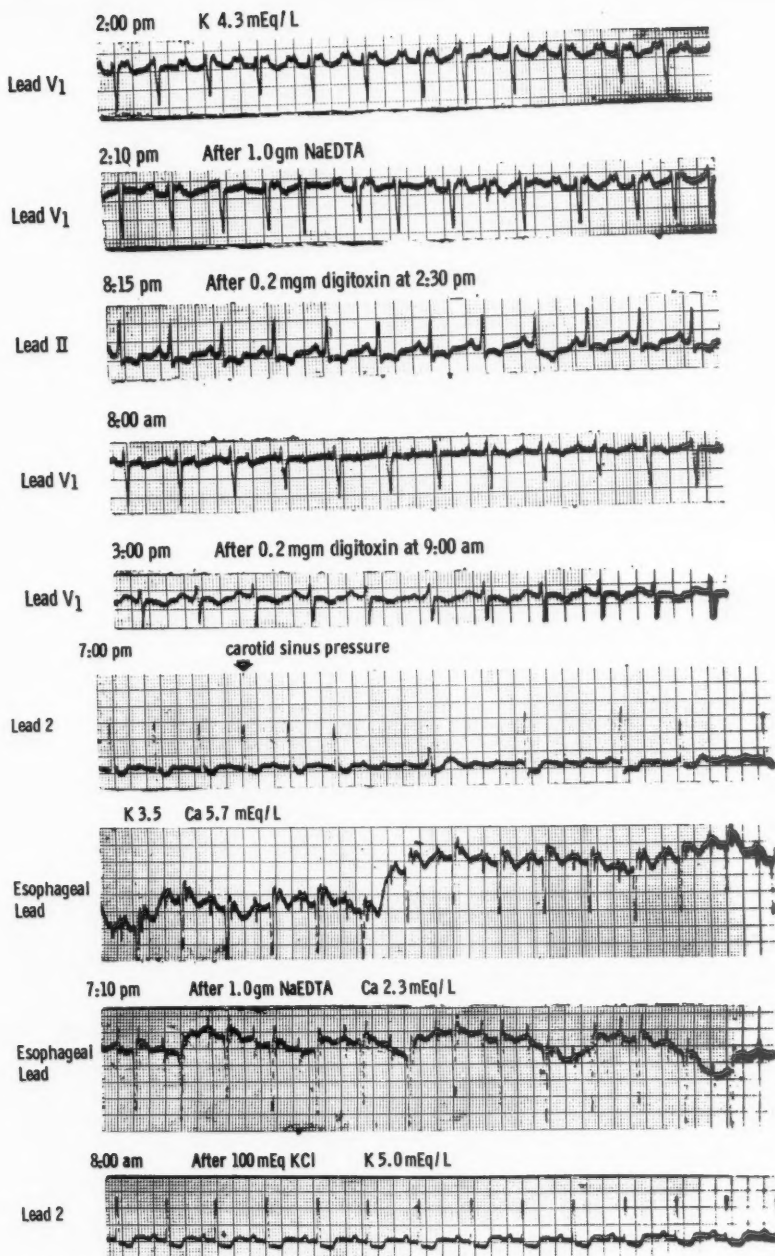


FIG. 2 Top. Electrocardiograms in patient H.B. showing atrial tachycardia with A-V block (2:00 p.m.) not responding to NaEDTA (2:10 p.m.). Six hours after further digitalis therapy, the electrocardiogram reverted to normal sinus rhythm (8:15 p.m.). Twelve hours later, atrial tachycardia recurred (8:00 a.m.), but again reverted to normal sinus rhythm 6 hours after additional digitoxin. Digitalis was continued without further incident.

FIG. 3 Bottom. Electrocardiograms in patient J.M. showing atrial flutter (7:00 p.m.) confirmed by esophageal lead. After NaEDTA produced no change in the arrhythmia (7:10 p.m.), the patient was given potassium chloride intravenously with reversion to normal sinus rhythm (8:00 a.m.). Thereafter he received 0.1 mg. of digitoxin daily without incident.

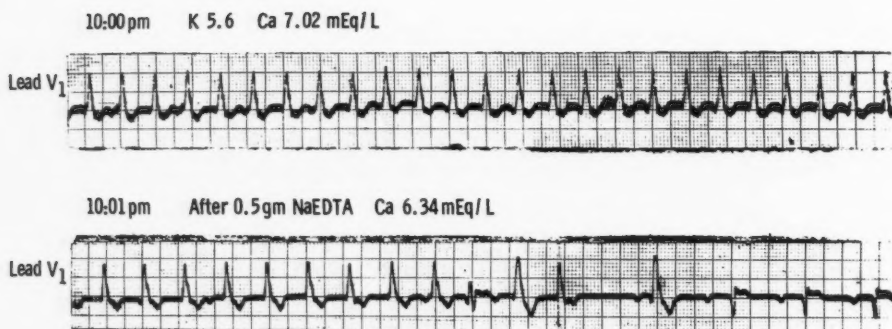


Fig. 4. Electrocardiograms in patient C.B., who developed transient first-degree heart block following digitalization. Subsequently on maintenance doses he showed ventricular tachycardia (10:00 p.m.). This reverted to normal sinus rhythm with first-degree heart block following NaEDTA (10:01 p.m.). Four days later, first-degree heart block was no longer present and digitalis was reinstituted without further complication.

employed. Blood samples from veins other than those used for NaEDTA injection were obtained before and after the test.

Plasma potassium was determined with a flame photometer with use of a lithium internal standard. Serum calcium was determined by the method of Sobel and Hanok<sup>14</sup> modified for semi-microtechnic; this procedure measures divalent ions and includes magnesium.

#### RESULTS

**Supraventricular Arrhythmias.** NaEDTA was administered to 6 patients with supraventricular arrhythmias. In all instances the arrhythmia was unchanged. The data are presented in table 1.

All the patients had received digitalis therapy and in 2 of these, the arrhythmia, atrial tachycardia with block, was thought to be the result of this therapy. In these patients, M.M. (fig. 1) and A.R., this rhythm was unchanged by NaEDTA therapy and reverted to normal sinus rhythm after the administration of potassium chloride. Patient H.B. also showed atrial tachycardia with block. Further digitalis therapy was associated with conversion of the arrhythmia to a sinus mechanism (fig. 2), indicating that digitalis intoxication was probably not a factor in its production.

Patient J.M., who had atrial flutter that did not change after NaEDTA therapy, reverted to normal sinus rhythm after administration of potassium chloride (fig. 3). Since it has been shown that potassium chloride

may be effective in the treatment of atrial flutter<sup>15</sup> and since atrial flutter is uncommon as a manifestation of digitalis intoxication, this arrhythmia was not considered due to digitalis.

Patient P.G. had atrial flutter and had received inadequate digitalis therapy. NaEDTA injection caused no change, and the rhythm subsequently converted to atrial fibrillation after more digitalis was administered. The final patient in this group, L.M., developed first-degree heart block after receiving 1.4 mg. of digitoxin in 24 hours. NaEDTA injection caused no change. First-degree heart block persisted during the time the patient was given maintenance digitalis therapy.

**Ventricular Arrhythmias.** NaEDTA was administered 8 times to 7 patients with ventricular arrhythmias (table 2). All but 1 patient had received digitalis and in 6 instances, this therapy was considered responsible for the arrhythmia. In 5 of these 6, ventricular tachycardia reverted to normal sinus rhythm during the administration of 0.5 Gm. or less of NaEDTA (figs. 4 and 5).

One patient (M.Z.) received NaEDTA on 2 occasions. On the first trial, NaEDTA administration was associated with correction of ventricular bigeminy although digitalis therapy was obviously inadequate at that time. On the second, ventricular bigeminy did not respond to NaEDTA administration

TABLE 1.—Results in Patients with Supraventricular Arrhythmias

| Patient,<br>age, sex        | Previous digitalis therapy  | Electrocardio-<br>gram before test                     | Dose of NaEDTA     | Electro-<br>cardiogram<br>after test | (mEq./L.<br>including<br>magnesium) |             |            | Plasma K<br>before test | Subsequent<br>KCl<br>therapy<br>(iv) | Plasma K<br>immediately<br>after KCl<br>therapy | Subsequent<br>digitalis<br>therapy    | Course   |
|-----------------------------|---|--|--------------------|--------------------------------------|-------------------------------------|-------------|------------|-------------------------|--------------------------------------|---|---------------------------------------|--|
|                             |   |  |                    |                                      | Serum<br>calcium                    | before test | after test |                         |                                      |   |                                       |  |
| M.M., 76, F<br>HCVD<br>ASHD | 1.2 mg. digitoxin, then 0.1<br>and 0.2 on alternate days<br>for 6 weeks   | Atrial tachy-<br>cardia with<br>block                  | 1.0 Gm. in 10 min. | No change                            | 6.55                                | 5.50        | 5.50       | 3.3                     | 40 mEq. in<br>12 hours               | 5.1 mEq./L.                                     | None                                  | See figure 1   |
| A.R., 80, F<br>ASHD         | 0.1 mg. digitoxin every 2<br>days for 4 years, then 1.2<br>mg. in 72 hours, followed<br>by 0.1 and 0.2 for 3 days | Atrial tachy-<br>cardia with<br>block                  | 1.2 Gm. in 12 min. | No change                            | 6.65                                | 5.50        | 5.50       | 3.9                     | 65 mEq. in<br>12 hours               | 4.9 mEq./L.                                     | None                                  | Reverted to normal sinus<br>rhythm, started on 0.1 mg.<br>digitoxin daily and discharg-<br>ed 9 days later |
| H.B., 83, F<br>HCVD         | 1.4 mg. digitoxin in 12<br>hours  | Atrial tachy-<br>cardia with<br>block                  | 1.0 Gm. in 10 min. | No change                            | —                                   | —           | —          | 4.3                     | None                                 | —   | 0.2 mg. digi-<br>toxin                | See figure 2   |
| J.M., 73, M<br>ASHD         | 0.1 and 0.2 mg. digitoxin<br>on alternate days for 4<br>months  | Atrial flutter   | 1.0 Gm. in 10 min. | No change                            | 5.70                                | 2.30        | 2.30       | 3.5                     | 100 mEq. in 5.0 mEq./L.<br>12 hours  | 5.0 mEq./L.                                     | None                                  | See figure 3   |
| P.G., 71, M<br>HCVD         | 0.1 and 0.2 mg. digitoxin<br>on alternate days for<br>several years, then none<br>for 2 weeks                     | Atrial flutter   | 1.5 Gm. in 15 min. | No change                            | 5.22                                | 4.42        | 4.42       | 5.4                     | None                                 | —   | 0.8 mg. digi-<br>toxin in 24<br>hours | Reverted to atrial fibrillation<br>with slow ventricular rate  |
| L.M., 69, F<br>ASHD         | 1.4 mg. digitoxin in 24<br>hours  | Normal sinus<br>rhythm with<br>1st degree<br>A-V block | 1.0 Gm. in 10 min. | No change                            | 6.95                                | 5.90        | 5.90       | 4.4                     | None                                 | —   | 0.1 mg. digi-<br>toxin daily          | Normal sinus rhythm with<br>1st degree A-V block per-<br>sisted to discharge 6 weeks<br>later              |

HCVD, hypertensive cardiovascular disease; ASHD, arteriosclerotic heart disease; RHD, rheumatic heart disease.

TABLE 2.—Results in Patients with Ventricular Arrhythmias

| Patient<br>age, sex                         | Previous digitalis therapy   | Electrocardio-<br>gram before test   | Dose of NaEDTA     | Electro-<br>cardiogram<br>after test                                  | (mEq./L.<br>including<br>magnesium) |            | Plasma K<br>before test | Subsequent<br>KCl<br>therapy<br>(iv) | Plasma K<br>immediately<br>after KCl<br>therapy | Subsequent<br>digitalis<br>therapy  | Course  |
|---|--|--|--------------------|---|-------------------------------------|------------|-------------------------|--------------------------------------|---|---|---|
|   |  |  |                    |   | Serum<br>calcium                    |            |                         |                                      |   |   |   |
|   |  |  |                    |   | before test                         | after test |                         |                                      |   |   |   |
| C.B., 83, M<br>ASHD                         | 1.2 mg. digitoxin, then<br>0.1 and 0.2 alternately<br>for 16 days  | Ventricular<br>tachycardia   | 0.5 Gm. in 1 min.  | Normal<br>sinus<br>rhythm<br>with 1st<br>degree<br>heart<br>block     | 7.02                                | 6.34       | 5.6                     | None                                 | —   | 0.1 mg. digi-<br>toxin daily, 4<br>days after test                              | See figure 4  |
| A.B., 79, F<br>HUCVD                        | 1.2 mg. digitoxin, then<br>0.1 and 0.2 alternately<br>for 10 days  | Ventricular<br>tachycardia   | 0.2 Gm. in 2 min.  | Normal<br>sinus<br>rhythm   | 5.20                                | 4.43       | 3.7                     | 40 mEq. in<br>1 hour                 | None  | None  | See figure 5  |
| E.J., 62, F<br>Cor<br>pulmonale,<br>sarcoid | 0.1 Gm. digitalis leaf for<br>2 weeks, then 1.0 Gm.<br>daily for 3 days  | Ventricular<br>tachycardia   | 0.4 Gm. in 4 min.  | Normal<br>sinus<br>rhythm   | 7.38                                | 6.80       | —                       | None                                 | —   | None  | Normal sinus rhythm per-<br>sisted 40 min. following 0.6<br>Gm. additional NaEDTA,<br>then ventricular tachycardia<br>recurred and patient died |
| D.P., 50, F<br>RHD                          | 0.1 and 0.2 mg. digitoxin<br>on alternate days for sev-<br>eral years, then 0.5 in 12<br>hours   | Ventricular<br>tachycardia   | 0.5 Gm. in 1 min.  | Atrial<br>fibrillation  | 7.18                                | 6.10       | 3.6                     | None                                 | —   | None  | Pulmonary edema and death<br>12 hours later   |
| E.C., 53, F<br>ASHD                         | 0.6 mg. ouabain and 1.4<br>mg. digitoxin in 72 hours,<br>0.1 and 0.2 alternately for<br>7 days, then an additional<br>0.2 mg. ouabain in 2 hours | Ventricular<br>tachycardia   | 0.4 Gm. in 4 min.  | Sinus<br>tachycardia<br>with A-V<br>dissocia-<br>tion                 | —                                   | —          | 4.9                     | None                                 | —   | None  | Died in pulmonary edema<br>and shock 1 hour later   |
| M.Z., 69, M<br>ASHD                         | 0.2 mg. digitoxin daily for<br>2 years, then 0.2 every 3<br>days for 1 month   | Atrial fibril-<br>lation with<br>frequent ven-<br>tricular pre-<br>mature con-<br>tractions,<br>bigeminy | 0.9 Gm. in 9 min.  | Atrial<br>fibrillation<br>with rare<br>premature<br>contrac-<br>tions | 6.02                                | 5.70       | 4.4                     | None                                 | —   | 0.3 mg. ouabain<br>in 3 hours, then<br>1.2 mg. digi-<br>toxin in 72<br>hours    | See figure 6  |
| Same<br>patient                             | See preceding  | Same rhythm<br>as pretest<br>EKG above   | 1.0 Gm. in 10 min. | No change   | 5.80                                | 5.50       | 4.2                     | None                                 | —   | 0.1 and 0.2 mg.<br>digitoxin on<br>alternate days                               | See figure 6  |
| J.D., 51, M<br>Cor pul-<br>monale           | None   | Ventricular<br>tachycardia   | 1.2 Gm. in 4 min.  | No change   | —                                   | —          | 3.4                     | None                                 | —   | 1.4 mg. digi-<br>toxin in 24<br>hours, then 0.1<br>and 0.2 on<br>alternate days | See figure 7  |

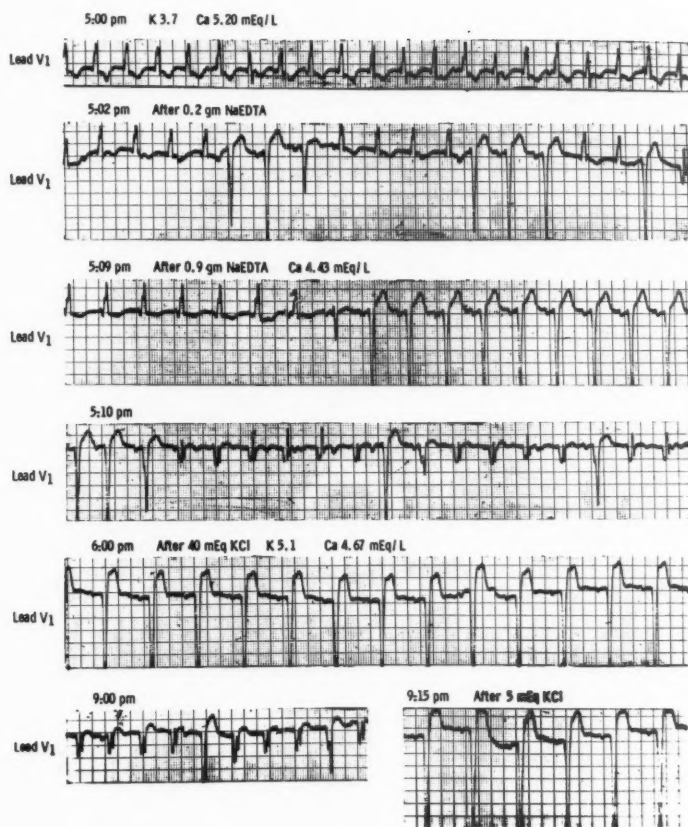


FIG. 5. Electrocardiograms in patient A.B. showing ventricular tachycardia (5:00 p.m.) following redigitalization. NaEDTA resulted in intermittent normal sinus rhythm (5:02 and 5:09 p.m.) which reverted to ventricular tachycardia following cessation of injection (5:10 p.m.). After potassium chloride intravenously, normal sinus rhythm recurred (6:00 p.m.). Later, the electrocardiogram again showed ventricular tachycardia (9:00 p.m.) which reverted to normal sinus rhythm following reinstitution of potassium chloride (9:15 p.m.). Normal sinus rhythm persisted for 3 days without further potassium or digitalis therapy. The patient died following a sudden episode of shock and pulmonary edema.

although digitalis intoxication was suspected. This paradoxical response is presented in detail:

M.Z., a 69-year-old man, had normal sinus rhythm with marked first-degree heart block (P-R interval of 0.52 second) in 1949. In 1956 he developed congestive heart failure and was treated with 0.2 mg. of digitoxin daily without an initial digitalizing dose. Eighteen months later, he was hospitalized for amputation of a gangrenous toe. Since the duration of first-degree heart block was not known, digitalis was withheld. One week later, an electrocardiogram revealed atrial fibrillation with a ventricular rate

of 50 per minute. Digitoxin was reinstituted at a dose of 0.1 mg. daily, to be administered only if radial pulse rates were more rapid than 60 per minute. On this schedule he received 0.1 mg. of digitoxin 2 to 3 times weekly.

During the first month of hospitalization, he had a weight gain of 9.9 Kg. and peripheral edema was noted, whereupon the dose of digitoxin was increased to 0.1 mg. daily. Over the next 3 days he was given mercurial injections without change in weight and then, 10.0 Gm. of ammonium chloride daily were administered by mouth. Electrocardiogram showed atrial fibrillation with a slow ventricular rate and premature ventricular contractions giving rise to bigeminy (fig. 6). A contin-

nous electrocardiogram during an injection of NaEDTA showed no change in the coupled rhythm over a 9-minute period until 0.9 Gm. had been administered. The bigeminy then disappeared and only occasional premature ventricular contractions were noted. Twelve hours later, however, he developed pulmonary edema without electrocardiographic change except for a slight increase in ventricular rate. During the succeeding 72 hours, 0.3 mg. of ouabain and 1.2 mg. of digitoxin were administered, following which ventricular bigeminy recurred. An additional 1.0 Gm. of NaEDTA administered in a 10-minute period produced no change in the arrhythmia. Following an injection of mercurial diuretic, his weight fell 2.8 Kg. in 18 hours. Electrocardiogram showed no further premature contraction and digitoxin was reinstituted at a dose of 0.1 and 0.2 mg. on alternate days without further incident.

A final patient, J.D., who had never received digitalis had ventricular tachycardia which did not respond to an injection of 1.2 Gm. of NaEDTA (fig. 7).

**Toxicity.** Toxicity to NaEDTA was not observed. In one instance (D.P.) ventricular tachycardia reverted to atrial fibrillation with a more rapid ventricular rate than that observed prior to the onset of the digitalis-induced ventricular tachycardia. Similarly in patient M.Z., the pulmonary edema that followed the first administration of NaEDTA may have been related to this therapy. It is suggested that the change in serum calcium may have led to a transient state of underdigitalization.

#### DISCUSSION

The use of rapidly injected NaEDTA appears to have greater value therapeutically than diagnostically. In 5 patients with digitalis-induced ventricular tachycardia, injection of NaEDTA was associated with reversal of the arrhythmia. In these patients relatively small doses of NaEDTA (0.5 Gm. or less) were effective. One patient with ventricular tachycardia, who had not received digitalis, did not revert after the administration of 1.2 Gm. of NaEDTA.

Ventricular arrhythmias unassociated with digitalis intoxication, however, may respond to NaEDTA (Case M.Z., trial 1). Gubner and Kallman<sup>12</sup> and Kabakow and Brothers<sup>13</sup> have also reported such instances. The latter investigators associated response with the pres-

ence of negative potassium balance. In the case reported herein, however, plasma potassium was normal and there was no suggestion of recent potassium loss.

Supraventricular arrhythmias failed to respond to NaEDTA in our study as well as that of Kabakow and Brothers. The arrhythmias were observed in all relationships to previous digitalis administration and plasma potassium levels. These results differ from those of Kabakow and Brothers, who thought that NaEDTA was effective in undigitalized patients with lowered potassium levels. It is noteworthy that the patient in whom they demonstrated this relationship had ventricular bigeminy and not a supraventricular arrhythmia. Gubner and Kallman reported 2 patients with atrial tachycardia with block who responded to infusion of NaEDTA. Potassium levels were not reported. Although the authors concluded that both these arrhythmias were supraventricular in origin, the abnormal configuration of the QRS complexes raises the possibility that they were ventricular. These results suggest that NaEDTA is unreliable, if effective at all, in the treatment of supraventricular arrhythmias no matter what the relationship to digitalis or potassium balance.

In general, we found a poor relationship between the dose of NaEDTA administered, the decrease in serum calcium produced, and the clinical response. NaEDTA was discontinued, however, when an effect was produced so that the patients who did not respond received larger doses of the drug. The occurrence of false positive and false negative results in ventricular arrhythmias, the lack of response in supraventricular arrhythmias, and the poor relationship between dose of NaEDTA and clinical or chemical response indicate that the response to NaEDTA injection is a poor guide to the degree of digitalization.

This defect does not preclude its usefulness in the therapy of ventricular arrhythmias. The use of procaine amide, quinidine, or potassium therapy may be dangerous in patients with irritative ventricular arrhythmias. NaEDTA can be administered with little danger

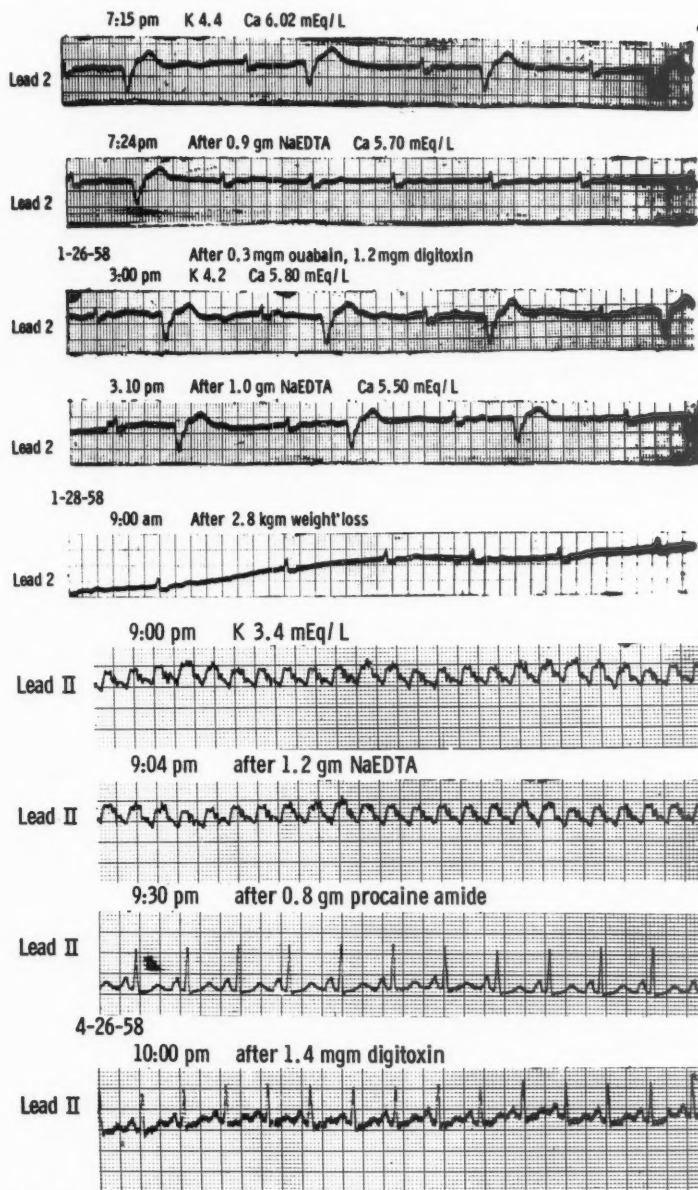


FIG. 6 Top. Electrocardiograms in patient M.Z. showing ventricular bigeminy and response to NaEDTA.

FIG. 7 Bottom. Serial electrocardiograms in patient J.D. showing ventricular tachycardia (9:00 p.m.). Digitalis had never been administered. NaEDTA produced no change in the arrhythmia (9:04 p.m.). Following 0.8 Gm. of procaine amide intravenously, the rhythm changed to normal sinus (9:30 p.m.). Signs of congestive heart failure, present initially, persisted following restoration of normal sinus rhythm and the patient was successfully treated during the next 24 hours with a 500-ml. phlebotomy and 1.4 mg. of digitoxin. He was discharged 4 days later on 0.1 and 0.2 mg. of digitoxin on alternate days and 1.5 Gm. of procaine amide daily.

and may be the drug of choice in those ventricular arrhythmias clearly due to digitalis intoxication in the absence of potassium loss. Even in the presence of hypopotassemia NaEDTA may be a useful emergency measure prior to potassium replacement. The possibility exists that in patients with congestive heart failure, NaEDTA may reverse the beneficial effects of digitalis and precipitate pulmonary edema (patient M.Z.). Smaller doses of NaEDTA should be used in such instances.

#### SUMMARY

In 14 cases of cardiac arrhythmia, the chelating agent, disodium ethylene diamine acetate (NaEDTA), was administered in an attempt to bind serum calcium rapidly and, thus, to restore the previous cardiac mechanism. In 5 cases of ventricular tachycardia resulting from overtreatment with digitalis, the use of NaEDTA proved successful therapeutically.

The response to NaEDTA injection is a poor guide to the degree of digitalization. False positive and false negative results have been observed in ventricular arrhythmias. Supraventricular arrhythmias did not respond to NaEDTA, irrespective of the status of digitalis therapy and potassium balance. Clinical and chemical response was unrelated to the dose of NaEDTA.

For these reasons, it is concluded that intravenous NaEDTA while unreliable as a test agent, is valuable in the treatment of digitalis-induced ventricular arrhythmias.

#### ACKNOWLEDGMENT

We are indebted to Mrs. Ruth Aronson and Miss Carolyn Register for their technical assistance. Mr. Julius Lugovoy, Senior Chemist at Bellevue Hospital, kindly performed the determinations of serum calcium.

#### SUMMARY IN INTERLINGUA

In 14 casos de arrhythmia cardiac, le agente chelatori dinatrium-ethylene-diamino-acetato (NaEDTA) esseva administrate con le objective de effectuar un ligation rapide de calcium seral e de restaurar assi le previe mechanismo cardiac. In 5 casos de tachycardia ventricu-

lar causate per excessos del dosage de digitalis, le uso de NaEDTA se provava un successo therapeutic.

Le responsa al injection de NaEDTA non es un satisfacente criterio pro le grado de digitalisation presente. Resultatos false positive e false negative ha essite observate in arrhythmias ventricular. Arrhythmias supraventricular non respondeva a NaEDTA, sin riguardo al stato del digitalisation e del balancia de kalium. Le responsas clinic e chimie esseva sin relation al dosage de NaEDTA.

Pro iste rationes, le conclusion es formulate que administrationes intravenose de NaEDTA es non digne de confidentia como test sed pretiose in le tractamento de arrhythmias ventricular inducite per digitalis.

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Vander, A. J., Malvin, R. L., Wilde, W. S., and Sullivan, L. P.: Localization of the Site of Action of Mercurial Diuretics by Stop Flow Analysis. *Am. J. Physiol.* 195:558 (Dec.), 1958.

The occlusion of a catheterized ureter for a brief period of time and the collection of urine via a polyethylene tube after the occlusion is released permits a comparison of proximal and distal tubular function. This type of experiment was carried out in dogs before and after the administration of mercurial diuretics. An osmotic diuresis was maintained by a constant infusion of mannitol. Intravenous administration of thimerin or meralluride caused at least a 50 per cent reduction in the mass of water and sodium reabsorbed by the proximal tubule during the brief period of occlusion. Reductions in water and sodium were equivalent, and the proximal tubule reabsorbate therefore had a sodium concentration similar to that of plasma. The mercurials did not alter the ability of the distal tubule to lower urinary sodium concentration during the period of ureteral occlusion. These studies suggest that the major effect of mercurial diuretics is on the proximal tubule and that their action may be to interfere with the passive reabsorption of sodium and water in this area of the nephron.

KAYDEN

## A Large Whale Heart

By GEORGE J. RACE, M.D., W. L. JACK EDWARDS, M.D., E. R. HALDEN, M.D.,  
HUGH E. WILSON, M.D., AND FRANCIS J. LUIBEL, M.D.

THE comparative cardiac anatomy and function of mammals larger than man has been the subject of several prior studies.<sup>1-4</sup> However, the opportunity to secure the very large heart of an adult male sperm whale (*Physeter catadon*)<sup>5</sup> weighing approximately 47,700 pounds and measuring 44 feet in length occurred during a visit to a whaling factory in Paita, Peru, in connection with a study of the cortex of the adrenal gland of large mammals. The whale was taken off the coast of Peru, latitude south 56 degrees 15 minutes, longitude west 81 degrees 32 minutes, in water of 21.2 degrees Centigrade, by a Peruvian whaling company.\* The animal was dissected 18 hours after death, and the heart preserved by freezing in dry ice until formaldehyde injection and submersion could be accomplished.

**General Considerations.** The heart including 1 foot of proximal aorta weighed 256 pounds or 116 Kg. when removed. The animal's weight was calculated by multiplying length by diameter squared divided by 2, the usual method of the whaling company, and was 21,708 Kg.; length was 13.4 M. and the diameter was 1.8 M.

A second heart weighing 1,600 Gm. was obtained from a fetus in utero, with a length of 2.1 M., diameter of 0.45 M., and calculated weight of 212 Kg. The fetus was discovered in a female whale, accidentally killed, that measured 9.4 M. in length, 1.6 M. in diameter, and had a calculated weight of 12,032 Kg.

The whale heart is a large globular organ lying in the normal position for all mammals.

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Supported by a research grant from the National Institutes of Health, U.S. Public Health Service.

\*Cia. Ballenera del Norte, an affiliate of Archer-Daniels-Midland Co., Minneapolis, Minn.



FIG. 1 Top. Adult whale, right ventricle, and tricuspid valve, 15-inch ruler under moderator band.

FIG. 2 Middle. Adult whale, right main coronary artery distal end (15-inch ruler).

FIG. 3 Bottom. Adult whale aortic valve and opened aorta. Innominate artery folded back, not opened. Note ostium of left coronary in midlower part of photograph.

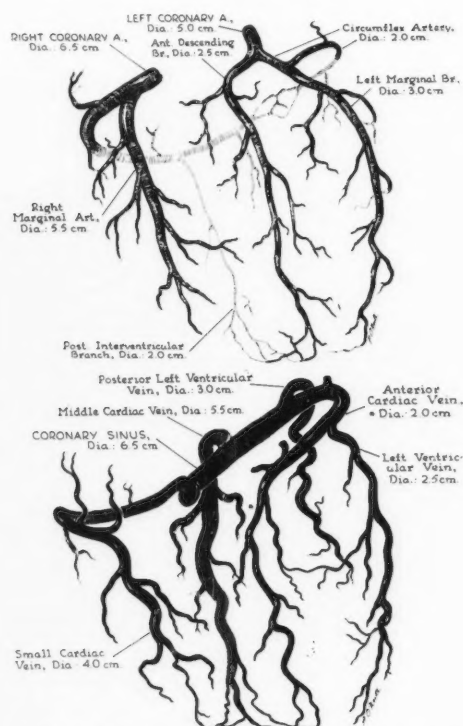


FIG. 4 Top. Adult whale, diagram of coronary arterial system.

FIG. 5 Bottom. Adult whale, diagram of cardiac venous system.

In the fetal heart a bifid apex was noted, while the adult heart had a single apex as in the human. The pericardium measured 0.5 cm. in thickness. The epicardium was smooth; a minimal amount of fat was visible in the atrioventricular sulcus. Both hearts were opened in the usual manner. The adult right ventricle (fig. 1) contained an estimated 10 L. of blood. No evidence of atherosclerosis or other disease was noted in the coronary arteries (figs. 2 and 3). Table 1 shows the measurements and their comparison with average human values.

**Coronary Artery and Venous Anatomy.** The distribution of coronary arteries and veins are illustrated in figures 4 and 5. The general similarities of whale and human circulatory anatomy can be noted, although there are several differences.

TABLE 1.—Anatomic Measurements of Hearts and Calculated Weight Ratios

|  | Adult male whale      | Fetal whale         | Average adult human   |
|--|-----------------------|---------------------|-----------------------|
| Body weight (Kg.)                          | 27,708                | 212                 | 75                    |
| Heart weight (Kg.)                         | 116                   | 1.6                 | 0.325                 |
| Left ventricular thickness (cm.)           | 6.3-12.5              | 2.1                 | 1.2                   |
| Right ventricular thickness (cm.)          | 3.1                   | 1.3                 | 0.3                   |
| Tricuspid circumference (cm.)              | 75                    | 15                  | 12.3*                 |
| Pulmonic circumference (cm.)               | 63                    | 10                  | 7.1*                  |
| Mitral circumference (cm.)                 | 68                    | 9.5                 | 11.0*                 |
| Aortic circumference (cm.)                 | 62                    | 9                   | 7.0*                  |
| Diameter coronary sinus (cm.)              | 6.5                   | 1.4                 | .8                    |
| Diameter left coronary ostium (cm.)        | 4.6                   | 0.25                | .3                    |
| Diameter right coronary ostium (cm.)       | 5.5                   | 0.5                 | .4                    |
| Diameter aorta (cm.)                       | 20                    | 2.5                 | 2.5                   |
| Average muscle fiber (diameter in microns) | 11.0 (Range 6.3-14.2) | 6.0 (Range 5.5-7.9) | 10.7 (Range 7.9-13.4) |
| Heart weight / Body weight Ratio           | .47%                  | .61%                | .43%                  |
| Cardiac output / Body weight Ratio         | 2.1%                  | —                   | 5.3%                  |

\*Gould, S. E.; Pathology of the Heart. Springfield, Ill., Charles C Thomas, 1953.

The left circumflex artery gives off a branch, called a left marginal branch in figure 4, which is actually larger in diameter than the continuing left circumflex. This supplies the major portion of the lateral mass of the left ventricle. Another difference is in the manner of anastomosis between the left circumflex artery and distal right coronary artery posteriorly; in the whale these arteries communicate by multiple, very small branches (fig. 4). The anterolateral right ventricle is supplied by a branch of the right coronary artery, the right marginal artery, originating 9 cm. from the ostium; the diameter of this branch is equal in size to the posteriorly cours-

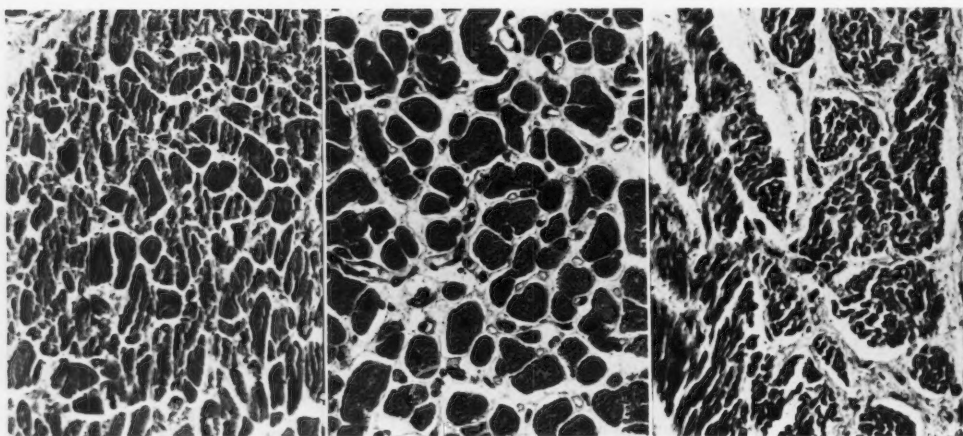


Fig. 6 *Left*. Microscopic adult whale heart. Note that fragmentation of fibers due to autolysis gives illusion that fibers are smaller than in human heart (table 1). Hematoxylin and eosin,  $\times 440$ .

Fig. 7 *Middle*. Microscopic adult human heart. Hematoxylin and eosin,  $\times 440$ .

Fig. 8 *Right*. Microscopic fetal whale heart. Hematoxylin and eosin,  $\times 440$ .

ing continuation of the right coronary. Multiple atrial branches, 1 cm. in size, from both coronary arteries were found.

There was no evidence of atherosclerosis or calcification in any arteries.

The fetal whale heart exhibited a disproportionately large right coronary artery, which directly anastomosed through a large artery with the left circumflex. The major ventricular myocardium branches of the left circumflex and right coronary arteries so prominent in the adult were relatively smaller in the fetal heart.

No major differences in venous return between whale and human heart were noted except for a large additional left ventricular branch (fig. 5).

*Conduction System.* By means of the method outlined by Widran and Lev,<sup>6</sup> a specific conduction system could not be grossly or microscopically differentiated. Microscopic sections of tissue from the area in which the atrioventricular node and bundle was sought showed extensive autolysis.

*Microscopic Anatomy.* Microscopic study of the adult whale heart from better preserved areas showed syncytial, striated muscle with fibers averaging  $11\ \mu$  in diameter (figs.

6 and 7 and table 1). It is of interest to note the small average diameter of the muscle fibers in the fetal whale heart (fig. 8). The human fetal heart is quite cellular, has small fibers, and enlarges by increase in fiber diameter after birth.<sup>7</sup> The same mechanism would appear to be present in the whale, although there would also have to be an increase in total numbers of myocytes as well as in fiber size to obtain the total mass of the adult whale heart.

Histologic sections of the adult whale aorta showed extremely thick, interlacing bundles of elastic and fibrous tissue (figs. 9-11). Smooth muscle was not demonstrated by trichrome stains except in smaller arteries of approximately 1 to 2 cm. diameter. These arteries showed a mixture of smooth muscle and elastic tissue similar to the human aorta. Smaller arteries were predominantly muscular as is the case in other mammals. There was no microscopic evidence of atherosclerosis, intimal fibrosis, calcification, or arteriosclerosis.

*Estimated Cardiac Output and Comparisons.* A comparison of ratios of heart weight to body weight of adult whale, whale fetus, and average human can be readily made from

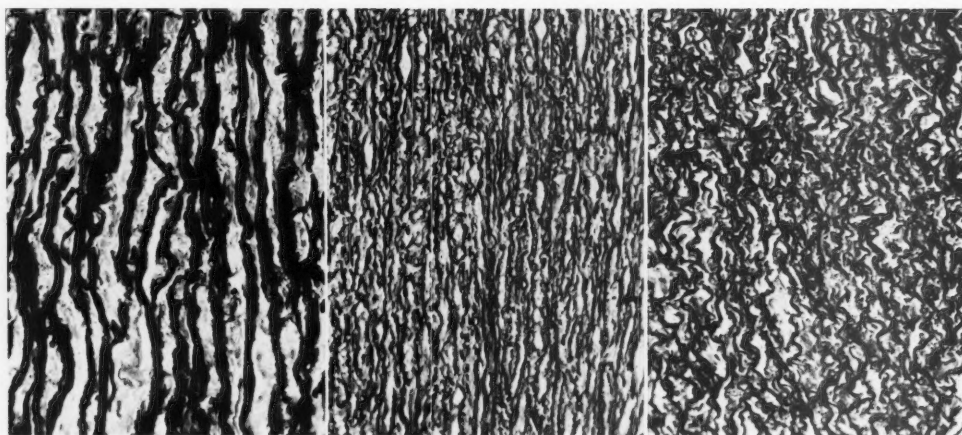


FIG. 9 *Left*. Microscopic adult whale aorta. Elastic tissue stain,  $\times 280$ .

FIG. 10 *Middle*. Microscopic adult human aorta. Elastic tissue stain,  $\times 280$ .

FIG. 11 *Right*. Microscopic fetal whale aorta. Elastic tissue stain,  $\times 280$ .

table 1. Since these ratios in table 1 are relatively constant, the linear increase of heart weight with increasing body weight in mammalian species is suggested.

An estimate of cardiac output in the adult whale was obtained in the following manner. The length of the left ventricular cavity before fixation from base to apex was 49 cm., and the ventricular cavity radius at the base was 21 cm. By means of the formula for a hemi-ellipsoid,  $V = 4/3(\pi abc) \div 2$ , the left ventricular volume of the adult whale was found to be 45.3 L. White et al.<sup>8-10</sup> have reported that the heart rate of a small Alaskan Beluga whale, estimated to weigh 1,136 Kg., varied from 12 to 24 beats per minute after harpooning. Assuming that the sperm whale has a slightly slower cardiac rate because of its much greater size (21,708 Kg.) a figure of 10 beats per minute was chosen arbitrarily, since the actual heart beat was not measured. At this assumed rate, the cardiac output would be a staggering 453 L. per minute with assumed complete ventricular emptying at each stroke. Similar calculation for the cardiac output of the fetal whale was not attempted because of the unknown factor of the fetal cardiac rate.

A comparison of ratios of cardiac output to body weight of whale and average man also

shows a remarkable similarity as seen in table 1.

#### SUMMARY

A large whale heart weighing 256 pounds (116 Kg.) was dissected. The coronary arteries had extremely large right and left marginal branches, which supplied the major lateral mass of the right and left ventricles. The venous system was similar to other mammals. Crude ventricular volume and cardiac output was calculated to be 453 L. per minute based on a rate of 10 per minute. The size of the cardiac muscle fiber was similar to the human myocardium except in a fetal whale heart (wt. 1,600 Gm.) in which very small fibers were found. The aorta was found to be 20 cm. in diameter and the wall to consist of very large interwoven bundles of elastic tissue and fibrous tissue apparently devoid of muscle. There was no evidence of arteriosclerosis. Comparative estimated cardiac output/body weight ratios and heart weight/body weight ratios were made between the whale and the human.

#### SUMMARIO IN INTERLINGUA

Un grande corde de balena de un peso de 256 libras (116 kg) esseva dissecate. Le arterias coronari habeva extremamente grande brancas dextero- e sinistro-marginal le quales

provisionava le major massa lateral del ventriculos dextere e sinistre. Le systema venose esseva simile a illo de altere mammiferos. Le volumine ventricular e le rendimento cardiac esseva calculate crudemente a 453 litros per minuta (super le base de un frequentia cardiac de 10 per minuta). Le dimensiones del fibrās myocardial esseva simile a illos in humanos. (Sed in un fetal corde de balena—de un peso de 1.600 g—micriissime fibras esseva incontrate.) Esseva constatate que le aorta habeva un diametro de 20 cm e que un pariete consistevt de grandissime fascies intertextite de histo elastic e histo fibrose, apparentemente sin musculo. Nulle signos de arteriosclerosis esseva notate. Comparative estimationes inter balena e homine esseva faeite pro le proportion de rendimento cardiac a peso corporee e pro le proportion de peso cardiac a peso corporee.

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**Weston, R. E., Grossman, J., Borun, E. R., and Hanenson, I. B.: The Pathogenesis and Treatment of Hyponatremia in Congestive Heart Failure. *Am. J. Med.* **25**:558 (Oct.), 1958.**

Primary retention of water and secondary hyponatremia were illustrated in metabolic studies of 3 subjects with rheumatic heart disease and congestive heart failure on a low-sodium intake in whom an imbalance between cardiac output and body needs was acutely intensified. In 1 case, this resulted from an escape from digitalization, in another from a severe respiratory infection and in the third from digitalis sensitivity due to potassium depletion. In each patient, an acute antidiuretic mechanism was invoked leading to retention of water in excess of sodium. Continued fluid intake during oliguria resulted in weight gain, increasing edema, azotemia, hyponatremia, and hypochloremia. These events were attributed to sustained production of antidiuretic hormone invoked by extraosmoreceptor mechanism when cardiac output became inadequate. Therapy should be directed toward increase of cardiac output by adequate digitalization or decreasing metabolic demands through treatment of infection. Misguided efforts to correct the assumed sodium deficit by intravenous administration of concentrated salt solution may further aggravate the condition.

KURLAND

## CLINICAL PROGRESS

### Clinical Evaluation of Chlorothiazide

By WALTER M. KIRKENDALL, M.D.

**C**HLOROTHIAZIDE, commercially available as Diuril, was introduced to the general medical profession January 1, 1958. It had been available to clinical investigators during the previous year. In this span it has won wide acceptance as an oral diuretic and antihypertensive agent. These comments should be considered in the light of this relatively brief experience.

The chemical structure of chlorothiazide is shown in figure 1. Chlorothiazide, acetazolamide, and sulfanilamide all have the sulfamyl group. As a result of this structural similarity, chlorothiazide, like sulfanilamide and acetazolamide, is an inhibitor of the enzyme, carbonic anhydrase. However, the ability of chlorothiazide to inhibit carbonic anhydrase plays only a small role in the drug's long-term action.<sup>1</sup>

Chlorothiazide is rapidly absorbed from the gastrointestinal tract and is well tolerated intravenously.<sup>2</sup> It is rapidly excreted by the kidneys, both by glomerular filtration and by tubular excretion. Approximately 30 to 50 per cent of the oral dose is excreted in 24 hours and over 90 per cent of the intravenous dose in 6 hours. Following oral ingestion, the drug is active for 6 to 12 hours and after intravenous administration for 2 to 4 hours.

From the Cardiovascular Research Laboratories, State University of Iowa College of Medicine, Iowa City, Iowa.

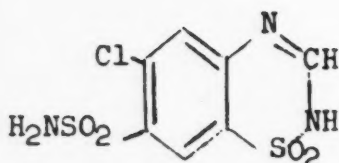
Presented, in part, at the Scientific Sessions for Clinicians at the 31st Annual Meeting of the American Heart Association in San Francisco, October 24, 1958.

The investigative work reported was supported by a grant from the U.S. Public Health Service, National Heart Institute no. H-3270.

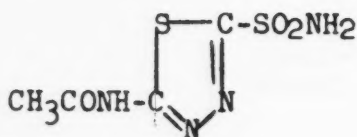
#### DIURETIC ACTION

The most noteworthy action of chlorothiazide is its ability to increase the urinary excretion of sodium, potassium, chloride, and water.<sup>3</sup> This increase may occur immediately after intravenous injection (table 1). The initial excretion of these electrolytes is accompanied by the diuresis of bicarbonate. After 24 hours bicarbonate excretion falls and the principal electrolytes excreted are sodium, potassium, and chloride. Figure 2 shows the effect of chlorothiazide on the excretion of water and electrolytes and on the composition of the blood. Immediately after the administration of 1 Gm. of chlorothiazide there was prompt weight loss, increased urinary output, a large increase in sodium, potassium, and chloride excretion. On the first day, bicarbonate excretion was elevated and the pH of the urine relatively alkaline. By the ninth day of therapy there was still a brisk diuresis of water, sodium, and chloride but little increase of potassium excretion over control levels. Bicarbonate excretion was much lower. There was a relatively constant serum sodium level, a slight fall in serum potassium, and no change in serum chlorides during this period. Carbon dioxide content of the serum had increased 3 mEq./L. during the study. During the posttreatment period, there was a prompt increase in body weight, a sharp retention of sodium and chloride, and a less remarkable retention of potassium. Serum electrolytes either returned toward normal or had stayed normal during the study.

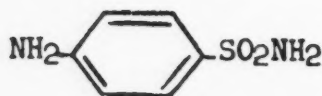
Long-term effects of chlorothiazide on body electrolytes in nonedematous patients have



Chlorothiazide



Acetazolamide



Sulfanilamide

FIG. 1. Structural formulas. Chlorothiazide has a heterocyclic and a benzene ring, the sulfamyl ( $\text{H}_2\text{NSO}_2$ ) group being on the benzene ring. Dihydrochlorothiazide (Esidrex) is a derivative of chlorothiazide, which is approximately 10 times as effective as a saluretic agent. This new compound has the double bond in the heterocyclic ring saturated by 2 hydrogen atoms.

been either a mild, long-term deficit or no change in exchangeable pools of sodium, potassium, and chloride.<sup>4</sup> Initially there is a tremendous loss of these elements. However, most of the deficits are replenished from the diet or from other electrolyte pools in the body. We have measured exchangeable electrolytes a number of times over 1- to 2-month periods in 5 patients receiving chlorothiazide, but our results are not conclusive. There is a tendency for initial electrolyte depletion to cease as therapy is continued. Although we usually detected some decrease in body elec-

TABLE 1.—Onset of Action of Chlorothiazide in Man

| Min.<br>in col.              | Urine<br>flow | Renal clearance (ml./min.) |      |      |
|------------------------------|---------------|----------------------------|------|------|
|                              |               | Na                         | Cl   | K    |
| 46                           | 4.3           | 0.9                        | 1.10 | 11.4 |
| Chlorothiazide, 250 mg. I.V. |               |                            |      |      |
| 3                            | 4.9           | 1.2                        | 1.47 | 14.5 |
| 3                            | 6.0           | 4.3                        | 2.66 | 26.1 |
| 3                            | 8.0           | 4.9                        | 3.64 | 39.2 |
| 4                            | 6.5           | 5.5                        | 5.46 | 40.8 |
| 22                           | 5.1           | 4.0                        | 3.76 | 32.7 |
| 24                           | 6.2           | 3.7                        | 3.98 | 36.9 |

Since the transit time from the kidney to the bladder is at least 2 to 3 minutes at these urine flow rates, the suggestive increase in flow and all clearances at 3 minutes and the definite increase at 6 minutes indicates that chlorothiazide acts immediately.

trolytes, the changes were small and tended to get smaller as treatment continued. Clinical effectiveness was maintained.

The mechanism of the diuretic action of chlorothiazide is not known. It is postulated that the drug interferes with sodium or chloride reabsorption in the proximal convoluted tubule of the kidney.<sup>1</sup> As a result of this interference, these electrolytes, plus water, are swept through the remaining portion of the nephron. Potassium may be exchanged for some of the sodium in the distal portions of the kidney. When the sodium ion is being avidly retained by the body, potassium is a relatively more important excretory product.

True tolerance to this drug does not seem to develop. There appears to be a level of depletion beyond which chlorothiazide is not active; if additional salt is given, it is excreted promptly. If one gives an extremely large dose of sodium chloride, the drug's effect may be overwhelmed and all the ingested salt will not be excreted.

When used as a diuretic agent in patients with edema, a 1-Gm. dose of chlorothiazide is about as effective as 2 ml. of meralluride (Mereuhidrin) given intramuscularly. The effectiveness varies from patient to patient. In our experience it has a wider range of use than the parenteral mercurials. Ford et al.<sup>5</sup> have shown that chlorothiazide is a much

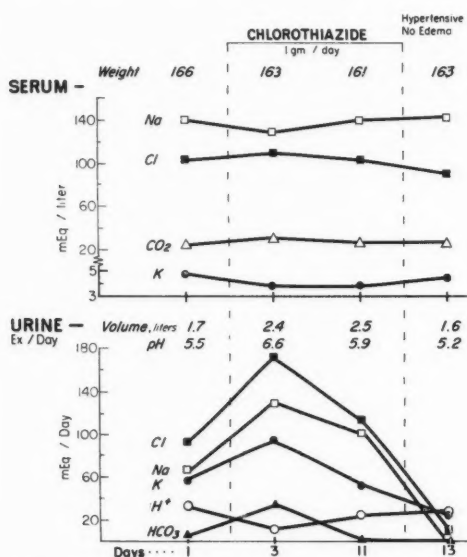


FIG. 2. Effect on body electrolytes and weight. Chlorothiazide was given during the period indicated by the dotted lines. The posttherapy values were obtained on the second day after chlorothiazide was discontinued. CO<sub>2</sub>, carbon dioxide content; H<sup>+</sup>, titratable acid; HCO<sub>3</sub>, bicarbonate.

more potent diuretic than any other currently available oral diuretic agent. [This includes aminometramide (Mietine), chloromerodrin (Neohydrin), acetazolamide (Diamox), amismetradine (Rolieton).]

In responsive patients the drug will continue to act until the body is free of edema. Figure 3 shows the weight loss of a patient with congestive heart failure after administration of chlorothiazide and maintenance of dry weight with a standard daily dose.

The diuretic action of chlorothiazide can be enhanced by the use of currently available carbonic anhydrase inhibitors such as acetazolamide.<sup>6</sup> In addition, its action can be potentiated by mercurial diuretics and at times there appears to be a synergistic effect between chlorothiazide and the mercurials. The chlorothiazide effect may be enhanced by drugs that compete with it for excretory enzyme systems, such as paraaminohippurate and by drugs that interfere with this excretory mechanism, such as probenecid (Benemid).<sup>2</sup>

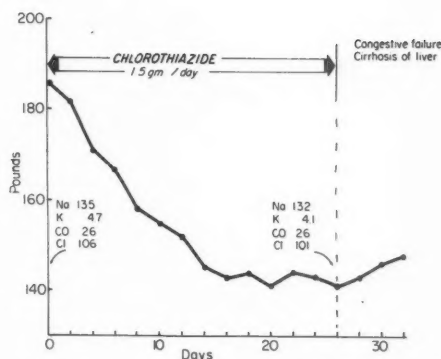


FIG. 3. Effect on body weight of patient with anasarca. Serum electrolytes are shown for pretherapy period and on the twenty-sixth day. On the fourteenth day "dry weight" was achieved and, despite the continued administration of chlorothiazide, no additional loss occurred. After chlorothiazide was discontinued, weight gain was at approximately the same rate as the loss. CO, carbon dioxide content of blood.

Chlorothiazide, alone or in conjunction with digitalis, is effective in removing the edema from over 80 per cent of our patients with congestive heart failure. It is of substantial benefit in removing edema from over half the patients with the nephrotic syndrome,<sup>7</sup> and it is equally effective in edematous patients with cirrhosis of the liver. It usually relieves premenstrual edema, and salt and water accumulation caused by steroid therapy. I have found it of considerable value in the control of localized collections of fluid, such as hypertensive encephalopathy. It has also been beneficial in such conditions as malignant exophthalmus.

Since this drug acts chiefly on the kidneys, its usefulness is limited if kidney function is poor. Nevertheless, it will help remove edema in persons with moderate to severe azotemia. It is not unusual to have an increase in blood urea nitrogen after the use of this drug in patients with uremia. This may be related to the mild depression in glomerular filtration rate and renal plasma flow reported by Crosley and Cullen<sup>8</sup> and observed by us.<sup>9</sup>

Chlorothiazide is indicated in the treatment of generalized edema if kidney and liver function and electrolytes are relatively nor-

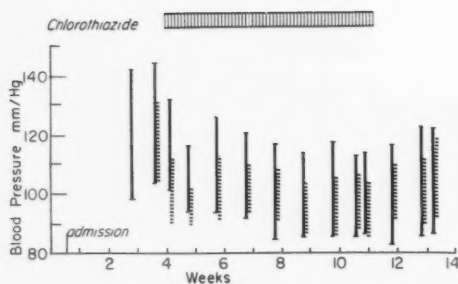


FIG. 4. Blood pressure response in patient treated with chlorothiazide alone. In this and subsequent illustrations *solid line*, blood pressure in the supine position, systolic at top, diastolic at the bottom; *barred columns*, blood pressure in the upright position depicted in the same fashion. Total daily dose of chlorothiazide, 1 Gm.

mal. It may be used in the face of these abnormalities if adequate precautions are taken.

Most patients with edema return to dry body weight with doses of 0.5 to 1 Gm. of chlorothiazide, daily or less frequently. At this dose, severe electrolyte disturbances are less common than with higher doses. Patients with initial potassium depletion and those who lose relatively large amounts of potassium (especially those on low-sodium diets) should have oral repletion of this ion with from 1 to 6 Gm. of a potassium salt daily. Larger amounts of chlorothiazide probably should be used for only short periods, although patients may tolerate 4 Gm. a day for as long as 3 months.<sup>9</sup>

#### ANTIHYPERTENSIVE ACTION

In 1948 Megibow and his associates<sup>10</sup> demonstrated that hypertension could be reduced by accelerated sodium depletion with mercurials. Nevertheless, at first chlorothiazide was not considered to be a hypotensive agent. Blood pressure lowering was not observed in laboratory animals. Soon after its introduction several investigators found that this drug often caused hypotension in hypertensive patients. A lively interest in the treatment of the hypertensive patient with chlorothiazide and other diuretics has developed.

Although a decrease in cardiac output after the acute administration of chlorothiazide

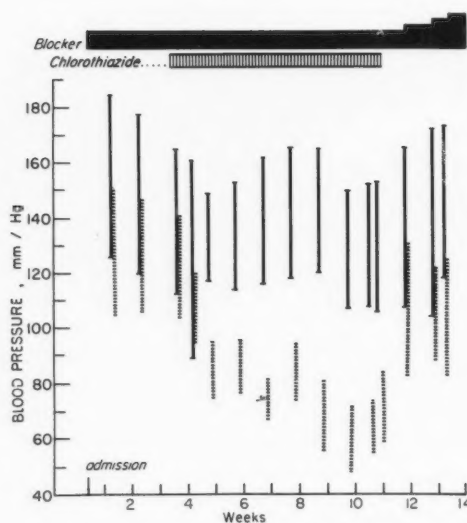


FIG. 5. Blood pressure response to addition of chlorothiazide in a patient receiving a ganglionic-blocking drug who had previously had a lumbar sympathectomy. Total daily dose of chlorothiazide was 1 Gm.

has been observed,<sup>11</sup> this is not thought to be the chief reason for its ability to reduce blood pressure. Peripheral resistance is lowered also. The following hypotheses have been presented to explain the hypotensive effect: (1) chronic depletion of the plasma volume, (2) mild sodium depletion, (3) redistribution of sodium and potassium within the compartments of the body, (4) the mild metabolic alkalosis which develops, (5) a direct effect of the drug on the central nervous system, or (6) on peripheral blood vessels. Most workers favor salt depletion or electrolyte redistribution, since other diuretics can produce the same effect and it can be prevented by adding salt to the diet.

The usual dose of chlorothiazide will not do much to "normal" blood pressure. Although there is a tendency for blood pressure to fall, it usually does not fall to hypotensive levels. Chlorothiazide alone will lower blood pressure in many hypertensive subjects but only about 10 to 15 mm. Hg mean pressure. Such a response is shown in figure 4. This fall in pressure, when it occurs, comes within

the first 1 to 2 days, is maximal within a week and is not necessarily orthostatic. There is a tendency to return to pretreatment level by the end of the first week after therapy is terminated. It may occur in patients with hypertension from any cause, including toxemia of pregnancy.

Chlorothiazide enhances the effect of Rauwolfia preparations, hydralazine, and veratrum alkaloids. The most spectacular results are seen when chlorothiazide is given with a ganglionic-blocking drug. A fall in mean supine pressure occurs but there is a more striking enhancement of the orthostatic drop. In figure 5, this orthostatic drop is shown when a blocking agent was administered with chlorothiazide in a patient who had had a lumbo-dorsal sympathectomy. The mean supine pressure was reduced only about 15 mm. Hg but the orthostatic pressure fell to levels incompatible with activity. Figure 6 shows a sharp fall in standing pressure in a patient with severe hypertension after the institution of chlorothiazide therapy, even though the dose of the blocking agent was decreased. Similar results occur in the sympathectomized patient without the addition of ganglionic blockers. As Sellers and his group<sup>12</sup> have reported, this is true also of adrenalectomized hypertensive patients.

We now have observed 6 hypertensive patients for 16 to 18 months and 40 patients for over 12 months who have had a good initial response to chlorothiazide therapy. Of these, the majority have continued to benefit from the drug. In many, objective signs of severe hypertensive disease have abated. Four have had myocardial infarcts during chlorothiazide therapy; and 2 of these died of rupture of the heart. Three patients, including 1 who had a myocardial rupture, died with progressive hypertensive disease. The remainder generally have looked and felt better than they did before we began chlorothiazide therapy.

Most of our patients are treated with 0.5 to 1 Gm. of chlorothiazide daily, for we have had very little success with intermittent therapy in hypertension. We advise that their

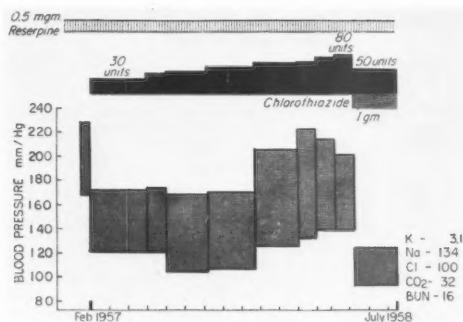


FIG. 6. Response in standing blood pressure in patient when chlorothiazide was added. Black area, indicated by units, represents a ganglionic-blocking drug; stippled areas, averages of home blood pressures taken by the patient. Drug doses are in total daily quantities. Despite the reduction of the dose of blocking drug by 40 per cent when chlorothiazide was added, the blood pressure fell sharply.

intake of sodium chloride be about 4 Gm. of salt a day. All patients on ganglionic-blocking agents are regulated with the aid of home blood pressure measurements and thus are controlled more easily and sent home earlier with safety.

When a patient is receiving a ganglionic-blocking drug and we wish to start chlorothiazide, we usually put him in the hospital or observe him very closely in our out-patient clinic. The dose of ganglionic-blocking drug is cut in half the day he starts therapy and necessary adjustments are made to keep the blood pressure within the desired range thereafter.

If a patient has not been treated with hypotensive agents and we wish to prescribe ganglionic-blocking drugs with chlorothiazide, we advise him to enter the hospital. Although these drugs may be started in the clinic, it is more convenient for both patient and physician, safer, and probably less expensive to have this period of close observation. Our usual plan is to prescribe chlorothiazide alone for 3 days. After breakfast on the fourth day, we give one oral dose of a ganglionic-blocking agent [2.5 mg. mecamylamine (Inversine), 20 mg. chlorisondamine (Ecolid), 20 mg. trimethidinium (Ostensin) or 25 mg. pentolinium (Ansolsen), the ratio between

TABLE 2.—*Frequently Observed Side Effects of Chlorothiazide Therapy*

|  |   |
|--|---|
| Hypokalemia                                  | } Usually transient and asymptomatic                                  |
| Hyponatremia                                 |   |
| Hypocholeremia                               |   |
| Metabolic alkalosis                          |   |
| Hyperuricemia                                |   |
| Azotemia                                     |   |
| Nausea and epigastric pain                   |   |
| Cardiac arrhythmias (digitalis intoxication) |   |
| Orthostatic hypotension                      | } Usually when given with ganglionic-blocking drugs or low salt diets |
| Weakness                                     |   |
| ? Weight loss                                |   |

these drugs being roughly 1:8:8:10] and observe the response with hourly blood pressure measurements. If orthostatic hypotension (below 130/90 mm. Hg) has not occurred by evening, we repeat the dose at 6:00 p.m. and continue the blood pressure measurements. If the patient's response is satisfactory, he is given 3 doses (after breakfast, at 2:00 p.m. and at bedtime) of the blocking agent on the fifth and sixth days. If the sitting pressure falls below 140/90 mm. Hg during this period, the next dose of the blocking agent is withheld or cut in half. After the sixth day, increases in dose of blocking agent ordinarily are indicated to keep the pressure within the desired range. When the patient leaves the hospital on the fifteenth day, he usually is taking the equivalent of 20 mg. of mecamlamine in divided doses. Subsequent adjustments of dosage are made after an out-clinic visit 2 weeks later, although the patient himself is instructed to change the dose of the ganglionic-blocking drug to maintain optimal blood pressure lowering. We strive to keep sitting blood pressures in the range of 140/90 mm. Hg in patients without azotemia, although this is not always possible because of orthostatic hypotension with symptoms. If reserpine is used as a third drug, we start this (maximal dose 0.5 mg.) on the first day of therapy. If hydralazine (Apresoline) is employed as an adjunct, it is begun on the twelfth day in a dose of 10 to 25 mg. twice daily. We gradually increase this for 2 weeks after the patient leaves the hospital, to a total of 200 mg. (less frequently 400 mg.) in 4 divided doses. Such a program avoids the in-

TABLE 3.—*Rare Side and Toxic Effects of Chlorothiazide Therapy*

|   |
|---|
| Skin rashes   |
| Hepatic coma (only in patients with severe liver disease) |
| Paresthesias of hands and feet                            |
| ? Myocardial infarction                                   |
| ? Iodine depletion (2 cases observed)                     |
| ? Metabolic acidosis (1 case reported)                    |
| ? Cholestatic jaundice (1 case reported)                  |

roduction of hydralazine while we are evaluating the patient's initial response to the blocking drug.

It is our custom to measure the blood urea nitrogen and serum potassium before and in the first week after beginning chlorothiazide therapy, repeating these tests after 3 and 6 weeks of therapy and thereafter at 12-week intervals. Approximately 6 months after the institution of therapy, we measure the serum uric acid, serum sodium and carbon dioxide content, or sooner if the patient does not appear to be doing well. We do not routinely give potassium supplements if the patient is receiving 1 Gm. or less of chlorothiazide daily and is eating well. If the serum potassium falls below 3.5 mEq./L. we supplement the diet with potassium salts each day. We have recognized no symptoms caused by potassium depletion in our hypertensive patients. Arrhythmias frequently do develop in our digitalized cardiac patients who have a considerable diuresis after chlorothiazide. It is possible that subtle changes occur in our hypertensive patients who have low serum potassium levels.

#### SIDE EFFECTS AND TOXIC REACTIONS

Besides potassium depletion, the side effects and toxic reactions shown in tables 2 and 3 have been reported. Sodium and chloride lowering have been noted. They may become important in some patients with edema but are seldom a problem in most of our hypertensive patients. The mild metabolic alkalosis which develops regularly does not appear harmful. We have ignored it.

Just as this drug may deplete, it may also disturb excretory mechanisms of the body as well. The occasional rise of nonprotein nitrogen probably is secondary to the known decrease in glomerular filtration rate. The transient increase in serum uric acid may be secondary to the drug's effect on enzyme systems in the proximal convoluted tubules of the kidneys. Neither of these forms of retention has been a problem in the management of patients except in those with very poor renal function. Usually the elevations disappear during therapy or very shortly after stopping the drug. One hesitates, however, to continue long-term treatment with chlorothiazide in the face of significant elevations of either of these values.

Nausea and epigastric pain are a problem in some patients but this is seldom severe enough to interrupt therapy. They may be responsible in part for the weight loss sometimes seen in nonedematous patients given chlorothiazide for long periods.

The orthostatic hypotension and weakness are almost always associated with the administration of ganglionic-blocking drugs but occasionally occur in patients with extremely low salt diets.

I have listed weight loss as a questionable side effect of chlorothiazide therapy, since in our group of hypertensive patients approximately one half have had a weight loss of 10 pounds after 6 months or more. We have not controlled other variables that might have caused patients to lose weight, but I have put this suggestion on the table primarily because the weight loss has been great in some patients in whom obesity was not a problem and whose calories were not restricted.

A toxic effect of chlorothiazide has been a maculopapular skin rash, which we have seen 4 times during the treatment of approximately 350 patients.

In some patients with liver disease, chlorothiazide precipitated hepatic coma or the triad of confusion, flapping tremor, and abnormal electroencephalographic changes.<sup>13</sup> Whether potassium loss is of primary importance is not known. Electrolyte imbalance is probably not the sole cause, since this state

can be prevented by the administration of broad spectrum antibiotics such as Neomycin.<sup>14</sup>

Paresthesias of the hands and feet have been reported<sup>15</sup> but are not a major problem.

The last 4 items are very difficult to assess. Wilkins<sup>16</sup> has suggested that myocardial infarction might be a complication of chlorothiazide therapy but he points out the difficulty of ascribing such vascular episodes to chlorothiazide. Although we have observed myocardial infarction, all patients had been severely ill with hypertension before the infarction and undoubtedly were poor risks. While theoretically the decrease in plasma volume might increase the likelihood of thrombosis, this has not been proved. The reduction of pressure, the decrease of cardiac work, the removal of edema and the increase in activity which most patients achieved should more than offset this risk.

The possibility of iodine depletion raises some interesting points. Certainly there are fundamental theoretical objections to the use of a drug that depletes the body of one or more of its elements. Although it is not proved unequivocally that the action of chlorothiazide is necessarily dependent on its ability to deplete the body of electrolytes and other materials, the possibility and probability exist. Thus, one should remember that other materials might be swept from the body as a result of interference with reabsorptive enzyme systems or secondary to the osmotic diuresis, which must occur in each nephron unit. It is possible, as with the mercurial diuretics, that certain water soluble vitamins might be swept from the body when water diuresis is brisk. Such materials as iodide, which may act much like chloride, may be carried through the kidney if chloride diuresis is pronounced. We have observed 2 patients who had an average increase in 24-hour uptake of radioiodine of over 30 per cent after 3 weeks of chlorothiazide therapy. This has not been a problem in long-term management of our patients, however, since we have found no significant increase in the uptake of radioiodine in 10 patients who received the drug for over 1 year.

Metabolic acidosis has been reported in 1 patient.<sup>9</sup> This appears to be a very rare complication and perhaps occurs with only significant or unusual degrees of renal failure.

A patient who developed a skin rash after chlorothiazide also developed a cholestatic type of jaundice similar to the type seen following the use of methyltestosterone and chlorpromazine.<sup>17</sup> No other such complication has been reported.

#### SUMMARY

In the 2 years chlorothiazide has been available, it has been demonstrated to have many of the characteristics of the ideal diuretic agent. It has become an important drug in the treatment of patients with edema and hypertension. Experience has indicated that the side effects and toxic reactions are not severe nor do they prohibit long-term use of the drug. In the vast majority of patients, clinical effectiveness has persisted for the duration of the study, up to 2 years in some and more than a year in many.

Chlorothiazide is a new type of powerful diuretic agent. Surely other similar compounds will be introduced. For these reasons, it is especially important that we understand its mechanism of action and shortcomings. Interest in the pharmacology of chlorothiazide already has brought us new information about certain fundamental problems of kidney function and systemic arterial hypertension.

#### SUMMARY IN INTERLINGUA

In le 2 annos del disponibilitate de chlorothiazido, illo se ha provate dotate de multes del characteristics del agente diuretic ideal. Illo ha devenite un importante droga in le tractamento de patientes con edema e hypertension. Le experientia ha monstrate que le effectos lateral e le reacciones toxic non es sever e non prohibi le uso prolongate del droga. In le grande majoritate del patientes, le efficacia clinic ha perdurate le periodo del studio, i.e. usque a 2 annos in certes e plus que un anno in multes.

Chlorothiazido es un nove typo de diuretico potente. Certo, altere simile compositos va

esser introduce. Pro iste rationes il es specialmente importante que nos comprende su mecanismo de action e su disadvantages. Le interesse in le pharmacologia de chlorothiazido ha jam produce pro nos nove informationes relative a certe problemas fundamental de function renal e de hypertension arterial in le circulation systemic.

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Mortimer, E. A., Jr., Vaisman, S. B., Vignau, A. I., Guasch, J. L., Schuster, A. C., Rakita, L., Krause, R. M., Roberts, R., and Rammelkamp, C. H., Jr.: The Effect of Penicillin on Acute Rheumatic Fever and Valvular Heart Disease. *New England J. Med.* **260**:101 (Jan. 15), 1959.

Since the initiating factor in acute rheumatic fever is infection by the Group A streptococcus, the authors attempted to alter the course of established rheumatic fever by eradicating the original inciting agent with penicillin. Forty-nine patients with acute rheumatic fever received an intensive 6-week period of penicillin treatment. The course of this group was compared with that of 48 patients who were not given antibiotics. All patients initially were treated with similar courses of aspirin for relief of symptoms. At the end of the 6-week period both treated and control patients were given 1,200,000 units of benzathine penicillin every 5 weeks for 1 year. Observations during the first 6 weeks of the illness in these patients showed no significant differences between the treated and control groups in regard to the acute clinical, laboratory, and electrocardiographic manifestations of the disease. Studies a year later, however, indicated a probable statistically significant reduction in the incidence of valvular heart disease in the penicillin-treated group. The difference between the effects of penicillin on the acute-phase manifestations of rheumatic fever and on the endocardial lesions suggests that these lesions may differ pathogenetically and also that the living streptococcus may continue to play a significant role in the development of valvular heart disease even after the symptoms of rheumatic fever have appeared. On the basis of these observations it is concluded that an intensive course of penicillin in addition to symptomatic therapy may be important in the treatment of acute rheumatic fever to reduce the incidence of later valvular damage.

SAGALL

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## ABSTRACTS

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### ATHEROSCLEROSIS

Jones, R. J., and Keough, T. F.: Factors in the Hypocholesteremic Response of Patients Given a Brain Extract. *J. Lab. & Clin. Med.* 52: 667 (Nov.), 1958.

A water and sorbitol emulsion of brain containing cerebroside and phospholipids was fed to 50 patients 4 times daily for 6 months. Serum cholesterol levels were measured for a control period of 6 to 8 months preceding the experimental period, and at semi-monthly or monthly intervals during the administration of the brain extract. The groups studied included 12 women and 38 men, ranging in age from 32 to 70 years, and including patients who had received anticoagulants because of embolic accidents secondary to rheumatic heart disease with atrial fibrillation; with essential familial hypercholesteremia; with clinical coronary artery disease with or without a history of myocardial infarction. The mean control level of serum cholesterol was reduced by the brain extract in 90 per cent of the patients. A direct correlation was found between the extent of the response and the height of the mean control level of the serum cholesterol and between the response and the dosage of brain extract administered. By relating the mean decrease in serum cholesterol to the mean control level of serum cholesterol, and the mean daily dose of the brain extract, it was possible to calculate the expected fall in the serum cholesterol in a given patient with a given serum cholesterol level who took a known daily dose of the emulsion. Since the relationship thus expressed was linear, it was concluded that the only variables that act on the decrease in the serum cholesterol are the initial control level of serum cholesterol and the daily dose of brain extract. Weight gain, which oc-

curred in 15 patients during the course of the experiment, was shown not to influence the hypocholesteremic response, since this response coincided with the anticipated fall. Nine patients who were known to have adhered faithfully to a low-fat diet showed a response 10 per cent greater than was anticipated. In 6 patients who had been previously studied for the hypocholesteremic response to the administration of  $\beta$ -sitosterol, the response to brain extract was shown to be quite comparable. It is believed that the brain extract has a physicochemical affinity for cholesterol based upon an adsorptive phenomenon that operates through restriction of intestinal reabsorption of cholesterol. Side effects of the brain extract were related chiefly to the gastrointestinal tract, the majority of patients noting a pleasant increase in bulk and softness of the stool.

MAXWELL

Tuna, N., Reckers, L., and Frantz, I. D., Jr.: The Fatty Acids of Total Lipids and Cholesterol Esters from Normal Plasma and Atheromatous Plaques. *J. Clin. Invest.* 37: 1153 (Aug.), 1958.

An analysis was made of the fatty acids of sterol esters and of total lipids (triglycerides), cholesterol esters, phospholipids, and free fatty acids, in normal plasma and atheromatous plaques. The "normal" material was obtained from 8 persons considered to be in good health and clinically free of arteriosclerosis. Plaques were studied from aortas obtained at autopsy. Neither qualitative nor gross quantitative differences between the total fatty acids of plasma and of the atheromatous plaques were found. In both blood and plaques, the linoleic acid content of cholesterol esters was relatively high. The ratio of linoleic to oleic acid was somewhat greater in

cholesterol esters of plasma than in those of plaques. The significance of this observation is not known. The authors interpret the data as supporting the concept that plaques are formed by filtration. Their findings are compatible with the notion of indiscriminate deposition of blood lipids in the arterial wall but do not prove it because of the possibility that compensating differences may exist in the various classes that make up the total lipids.

WAIFE

Schettler, G., Eggstein, M., and Jobst, H.: **Essential Hyperlipaemia**. *German M. Monthly* 3: 310 (Oct.), 1958.

Serum lipid studies, clinical data, and results of treatment of 30 patients with essential hyperlipemia are presented. In all patients characteristic increases were found in the amount of neutral fats in the serum. This was often associated with a less marked increase in phospholipids and cholesterol. Diagnostic lipoprotein patterns were obtained by electrophoretic and ultracentrifugal studies. Of the 30 patients, 25 showed clinical signs of arteriosclerosis even though only 2 patients were over 60. The association of hyperlipemia with gout or hypertension favored early and severe arteriosclerotic changes. The favorable therapeutic response of hyperlipemia to heparin suggested an etiologic relationship to the plasma clearing factor. Good therapeutic results were found in some patients following ACTH injections. In all instances a good therapeutic response with decrease in serum turbidity, fall in neutral fat concentration, regression of xanthomata, decrease in hepatomegaly and splenomegaly and disappearance of abdominal colic were found with an individually adjusted low-calorie low-fat diet. This response could be reversed by the addition of small amounts of saturated fats or natural fats with saturated fatty acids, whereas oils with high concentrations of doubly unsaturated fats acted favorably.

SAGALL

Beaumont, J.-L., Beaumont, V., Boumard, B., and Lenégre, J.: **Atherosclerosis and Primary Hyperlipemia** (On the Basis of 8 Observations). *Arch. mal. coeur* 51: 812 (Sept.), 1958.

Of 1,000 patients subjected to a study of serum lipids, 8 showed primary hyperlipemia not caused by diabetes or myxedema. Angina pectoris was present in 7, and in 3 of these the attacks appeared predominantly after meals. In 4 patients myocardial infarction and in 2 patients intermittent claudication was present. In 2 patients cholesterol and  $\beta$ -lipoproteins were elevated, and could not be influenced by diets poor in fats and

other antilipemic measures; both had tendinous xanthomas. Six patients had elevation primarily of neutral fats; in these, reduced fat diets and heparin caused diminution of hyperlipemia.

LEPESCHKIN

Miller, D. C., Trulson, M. F., McGann, M. B., White, P. D., and Stare, F. J.: **Diet Blood Lipids and Health of Italian Men in Boston**. *Ann. Int. Med.* 49: 1178 (Nov.), 1958.

A group of 189 men, aged 20 to 50, whose parents had been born near Naples, but who themselves had lived all their adult lives in the United States were studied and compared to a normal group of Neapolitan men. The serum cholesterol level of the Naples group was lower (mean 185 mg. per cent) than that of the Boston group (mean 239 mg. per cent). Fat provided about 20 per cent of the calories in the diet of the Naples group but about 41 per cent of the calories in the Boston group. Analysis of the serum lipids of the Boston group and tabulation of the dietary habits did not establish any satisfactory correlations. The subjects with a higher intake of unsaturated fatty acids appeared to have a lower serum cholesterol, but it also appeared that men who derived a smaller proportion of their calories from fat had a slightly higher blood lipid content. Tabulations of age, obesity, body build, and degree of physical activity with serum lipids showed varying degrees of correlation. Cigarette smoking, family history of cardiovascular disease or diabetes, electrocardiographic abnormalities, and elevated blood pressure were also plotted against serum cholesterol levels. It was not possible to predict who among the men will develop coronary artery disease, but it is planned to follow this group and periodically reevaluate them.

KAYDEN

## BLOOD COAGULATION AND THROMBOEMBOLISM

Boyles, P. W.: **A Method for the Induction of Segmental Radio-Opaque Blood Clots**. *Am. J. Clin. Path.* 30: 423 (Nov.), 1958.

Intravascular coagulation was produced in isolated superficial veins of anesthetized dogs by the injection of a mixture of equal volumes of human brain thromboplastin and a radiopaque medium (Dionosil). Prior to injection, the vein was tied proximally with a silk suture and the vein was occluded distally with a rubber tourniquet. The time for injection was 5 minutes, and occlusion was maintained for an additional 5 minutes. The size of the clot was determined by the length of the occluded vein. X-ray examination of the

extremity revealed the size and configuration of the clot. Serial x-ray examinations revealed that the clot slowly disappeared during a 10-day period.

KAYDEN

**Penick, G. D., Roberts, H. R., Webster, W. P., and Brinkhous, K. M.: Hemorrhagic States Secondary to Intravascular Clotting.** *Arch. Path.* 66: 708 (Dec.), 1958.

This study was an attempt at experimental verification of the hypothesis that in those conditions associated with intravascular clotting and associated also with a secondary hemorrhagic state, increased thromboplastic activity from whatever the cause accelerates intravascular coagulation, thereby producing deficiency of the clotting factors, which then results in a bleeding tendency. To hemophilic dogs, dogs treated with bishydroxycoumarin, dogs in whom liver injury was induced by chloroform administration, and control dogs, one of two types of thromboplastin was administered intravenously. The 2 materials were: crude tissue extracts regarded as complete thromboplastins and ultracentrifuged preparations regarded as partial thromboplastins. The normal dogs exhibited reaction patterns of neuromuscular and cardiorespiratory disturbances and had thrombocytopenia, hypoprothrombinemia, hypofibrinogenemia, and depressions in the anti-hemophilic activity of their plasma. These changes were all much less marked in the dogs with coagulation defects. The chloroform-treated animals were the most resistant to the thromboplastins and were able to tolerate larger doses. The resistance of the hemophilic dogs could be partially overcome by administration of the crude tissue extract. During the course of these experiments activation of profibrinolysin was also studied but could not be consistently demonstrated. The results of these experiments are thought by the authors to be consistent with the hypothesis that intravascular coagulation and resultant consumption of clotting factors are the basic mechanisms leading to a bleeding tendency.

MAXWELL

**Johnston, C. L., Jr., Ferguson, J. H., O'Hanlon, F. A.: Surface Activation of Plasma Clotting: A Function of Hageman Factor.** *Proc. Soc. Exper. Biol. & Med.* 99: 197 (Oct.), 1958.

Asbestos treatment of plasma produced activation (clotting-time acceleration) in normal and AHF (antihemophilic factor), PTC (plasma thromboplastin component), proconvertin, prothrombin, proaccelerin, and Stuart-deficient plasmas. Hageman-deficient plasma was not activated by comparable treatment. Purified Hageman-fac-

tor preparations from normal sera simulated activation, whereas preparations from sera of Hageman-trait patients were inactive in the same test system. The phenomenon of surface activation resulted from Hageman-factor activation and was not due to inhibitor adsorption. Asbestos treatment of plasma may be used as a presumptive test for the Hageman trait.

KRAUSE

**Maglagan, N. F., Billimoria, J. D., and Curtis, C.: Lipaemia and Blood Coagulation.** *Lancet* 2: 865, (Oct.), 1958.

A modification of the customary Stypven-technique was developed for the study of the influence of lipemia on clotting. As little as 14 Gm. of fat, irrespective of its nature, produced a substantial lowering of the Stypven clotting-time in 9 volunteers and larger amounts produced drops of up to 50 per cent. There was a striking correlation between the drop in Stypven time and the degree of lipemia. The chief difference in technique from previous studies consists in the simultaneous addition of calcium chloride and Stypven. If there is delay between the addition of Stypven and calcium, the lipolytic action of Stypven results in the production of considerable lysophosphatides, which lengthen the clotting-time. More lipolysis occurs with lipemic plasma than with fasting plasma, so that the accelerating effect of lipemia on the clotting time is partly masked.

KURLAND

**Kliman, A., and McKay, D. G.: The Prevention of the Generalized Schwartzman Reaction by Fibrinolytic Activity.** *Arch. Path.* 66: 715 (Dec.), 1958.

These experiments were designed to confirm the finding that the activation of fibrinolytic activity by streptokinase prevented the formation of thrombi occurring during a generalized Schwartzman reaction, but that preformed thrombi were not destroyed by the streptokinase. There were 4 groups of rabbits. The first control group underwent the induction of the Schwartzman reaction in the usual manner with Shear's polysaccharide. The first test group was treated in the same fashion except that 30 minutes after the second injection of toxin they were given streptokinase and streptodornase intravenously. Another control group received streptokinase only and the other test group received a single injection only of the polysaccharide followed in 30 minutes by an injection of streptokinase. The use of streptokinase after the second injection of endotoxin completely prevented the appearance of bilateral renal cortical necrosis, although,

there was virtually no effect on the extent of thrombosis in the lungs, liver, and spleen. When streptokinase was given immediately after the first injection of endotoxin, there is a significant reduction in the number of thrombi in the liver, spleen, and lungs when compared to a group that received a single injection of endotoxin only. The authors conclude that increased fibrinolytic activity must be present during the period when the thrombi are forming in order to exert a lytic effect, and that the increased fibrinolytic activity accomplishes a prevention rather than a reversal of the Shwartzman reaction.

MAXWELL

**Sokal, J. E., Ambrus, J. L., and Ambrus, C. M.: Treatment of Thrombosis with Fibrinolysin (Plasmin).** *J.A.M.A.* 168: 1314 (Nov. 8), 1958.

In extension of previous experimental studies which demonstrated that intravenously infused fibrinolysin caused lysis of clots in animals, the authors administered various preparations of fibrinolysin to 37 patients, most of whom had terminal carcinoma with complicating thromboembolic phenomena. The side effects of administration (malaise, nausea, tachycardia, cutaneous vasoconstriction, chills and fever) were decreased when purified preparations of human profibrinolysin activated with streptokinase or urokinase were used. Thirteen episodes of peripheral thrombophlebitis were treated with fibrinolysin infusions, nursing care, bed rest, foot cradle, sedatives and in 6 cases anticoagulants. In 5 of 8 cases in which the process was 3 days old or less when therapy was instituted, there was complete resolution; while in older processes there was complete resolution in 1, improvement in 2 and no effect in 2. The favorable responses were fairly uniform in that pain was found to disappear within 24 hours followed by a more gradual improvement in color, tenderness, and edema of the affected part. One patient in whom a skin flap became cyanotic was treated with intravenous fibrinolysin with apparent success as was an instance of probable venous thrombosis in the head and neck. Two patients with arterial thrombosis and embolism were treated without significant improvement. Several patients given fibrinolysin suffered recurrence of thrombosis soon after completion of the treatment; and since this compound does not prevent the formation of new thrombi, the authors believe that anticoagulants and fibrinolysin should be administered together. Emphasis is given to the experimental nature of this approach to the treatment of acute thrombosis.

FREEDBERG

## CONGENITAL ANOMALIES

**Weinstein, A.: Congenital Heart Disease in Successive Generations.** *J. Chron. Dis.* 8: 669 (Dec.), 1958.

The author comments upon the paucity of information which is available to suggest inheritance of congenital cardiac defects. The literature is reviewed, and 2 cases of atrial septal defect are presented. The first is in a 63-year-old woman with a diagnosis proved at autopsy, and the second is her 31-year-old son who had a successful repair of his cardiac lesion. With the exception of a 37-year-old brother of the son, there was no evidence of congenital cardiac defects in any other members of the family either in preceding or succeeding generations. This brother had an inconstant apical systolic murmur, but neither symptoms nor signs of cardiac disease. The author suggests that the study of the incidence of congenital heart disease in successive generations may be a fruitful one in view of the improvement in the surgical treatment of congenital heart disease which is restoring many patients to health and potential parenthood, thereby permitting some determination as to what extent congenital heart disease is an inherited defect.

MAXWELL

**Scott, R. C., McGuire, J., Kaplan, S., Fowler, N. O., Green, R. S., Gordon, L. Z., Shahetani, R., and Davolos, D. D.: The Syndrome of Ventricular Septal Defect with Aortic Insufficiency.** *Am. J. Cardiol.* 2: 530 (Nov.), 1958.

Seven instances of this syndrome, 2 of which were proved anatomically, have been detected clinically by the authors during the past 4 years. The ages ranged from 5 to 37 years and 4 were males. Six had effort intolerance, and congestive heart failure occurred in 4; none was cyanotic. Examination regularly showed peripheral signs of aortic insufficiency. All had enlarged hearts, and left ventricular hypertrophy predominated. There were loud systolic and diastolic murmurs heard best at the mid-left sternal border; in 1 a continuous murmur was heard. Fluoroscopy revealed moderate to marked enlargement of the heart, pulmonary artery and vasculature, and the aortic arch. The electrocardiogram showed left ventricular hypertrophy in 3, combined ventricular hypertrophy in 3, and right bundle-branch block in 1. Cardiac catheterization, prolonged in 6 patients, disclosed moderate pulmonary hypertension and increased blood oxygenation at the right ventricular level. The 22 reported autopsy-confirmed examples of this condition were summarized. The basic lesion was a high ventricular

septal defect associated with a deformity of 1 or more aortic cusps with or without dextro-position of the aorta. The differential diagnosis from the numerous resembling lesions, particularly patent ductus arteriosus, was discussed with emphasis on the importance of cardiac catheterization and, occasionally, of special roentgen procedures. The authors believe that this syndrome can usually be correctly diagnosed. Surgical correction has been attempted once, but unsuccessfully.

ROGERS

**Sambhi, M. P. and Zimmerman, H. A.: Pathologic Physiology of Lutembacher Syndrome.** *Am. J. Cardiol.* 2: 681 (Dec.), 1958.

The history of this uncommon syndrome is traced and the term now may properly include the combination of an atrial septal defect with shunting plus a significant mitral valve deformity whether stenotic, regurgitant, or both. The mitral lesion tends to increase the left atrial pressure which, however, is at least partly decompressed by shunting into the right atrium. Hence the shunt is larger than should be expected in the absence of a mitral lesion. The congestive phenomena, which may occur retrograde to the mitral deformity, involve the liver and great veins rather than the lungs. The late development of pulmonary vascular obstruction may result in a reduction of the left-to-right shunt, but cyanosis does not often occur. Possible beneficial influences of the septal and mitral defects on each other are discussed in an effort to account for the survival of some patients up to age 81 years. Yet, the combination of lesions usually produces a shorter life span than should be anticipated from either lesion alone. Surgical correction by an open technic is recommended.

ROGERS

**Downing, D. F., Grotzinger, P. J., and Weller, R. W.: Coarctation of the Aorta.** *J. Dis. Child.* 96: 711 (Dec.), 1958.

The literature is reviewed and 3 additional patients are presented who illustrate a possible complication of the successful treatment of coarctation of the aorta. Necrotizing arteritis of the small vessels in the tissues supplied by the aorta distal to the coarctation is probably, in part, due to a sudden increase in blood pressure in these areas. The authors emphasize the importance of a careful evaluation of any postoperative abdominal signs or symptoms. If bowel damage is suspected clinically, prompt laparotomy and resection of the involved portion of the intestine are recommended. The authors note

the use by other groups of antihypertensive agents in this condition but recommend caution in their use until their efficiency has been fully determined.

KARPMAN

**Carleton, R. A., Abelman, W. H., and Hancock, E. W.: Familial Occurrence of Congenital Heart Disease: Report of Three Families and Review of the Literature.** *New England J. Med.* 259: 1237 (Dec.), 1958.

Clinical and physiologic studies of 9 patients with congenital heart disease found among 3 families with 113 persons are reported. In each of 2 families, 3 patients with interatrial septal defect were found. The authors also reviewed the literature of multiple familial congenital heart disease since 1941, the beginning of the cardiac-catheterization era, and collected 141 such families, including 4 families with more than 1 case of atrial septal defect. They conclude from this study that although environmental gestational factors may sporadically be causative, the unusually high prevalence of congenital heart disease in the 3 families of this study appears to conform best with a single, recessive, autosomal mode of genetic transmission.

SAGALL

### CORONARY ARTERY DISEASE

**Lippschutz, E. J., and Maloney, M. C.: Hemopericardium and Cardiac Tamponade from Rupture of Heart and Aorta.** *New York State J. Med.* 23: 3815 (Dec. 1), 1958.

Thirty-one cases of cardiac tamponade and myocardial rupture were reviewed from postmortem data. The incidence of cardiac rupture was slightly greater in patients who were on anticoagulant therapy. The left ventricle was the most common site of rupture, and tears in the anterior wall occurred twice as frequently as those in the posterior wall. Of the 31 patients with a ruptured heart, 16 had hearts where left ventricular myocardium was 2 cm. or greater. Myocardial rupture was the result of coronary artery disease with myocardial infarction in all cases and occurred with increased frequency beyond 60 years of age. Rupture of the heart occurred most commonly between 4 and 10 days after the acute myocardial infarction. It was not possible to document accurately the degree of hypertension and its possible role in all cases. However, it has been observed that patients who display a persistent hypertension postinfarction are 3 times more likely to develop cardiac rupture than those who have normal blood pressures. No relationship could be ascertained between rupture of the

heart and the degree of type of physical exertion. When anticoagulant medication is used, clinical evidence of hemorrhagic pericarditis (such as prolonged, persistent or recurring friction rub, recurrence of cardiac pain or vascular collapse accompanied by distended neck veins) should be sought. When this occurs, pericardial tap and drainage should be accomplished.

KRAUSE

**Baron, D. N., Alexander, C. P., Bell, J. L., and Oakley, C. M.: Serum Transaminase Estimation in the Investigation of Myocardial Infarction.** *Quart. J. Med.* 27: 533 (Oct.), 1958.

A study of the serum glutamic-oxaloacetic transaminase (GOT) was made in 170 patients to assess the value of its estimation in the diagnosis and prognosis of myocardial infarction. The mean value in 25 normal subjects was 16 units (range 8-25). There was little daily variation or alteration with meals or exercise. Of 71 patients with unequivocal myocardial infarction, high levels were found in 49, borderline levels in 4, and normal levels in 18. In the first 12 hours, normal levels were sometimes found; between 12 and 48 hours, raised levels were always present; after 48 hours, normal levels were again sometimes present. It is thus significant that, of the 22 patients in this group with normal or borderline values, in 13 the blood was taken 8 days or more after the clinical onset and in 3 before 12 hours had elapsed. In 10 patients with a provisional diagnosis of myocardial infarction, serum transaminase levels were raised in all at least once. In 7 of 21 patients with angina, the levels were raised but not above 40 units. Twelve patients suffered pulmonary embolism; in 5 without shock, no elevation was found. In the remaining patients who had chest pain without evidence of infarction, the transaminase was always normal. Elevated values were also found on occasion in liver disease, acute pancreatitis, myositis, myocarditis, and ruptured kidney.

KURLAND

**Brown, D. F., McGandy, R. B., Gillie, E., and Doyle, J. T.: Magnesium-lipid Relations in Health and in Patients with Myocardial Infarction.** *Lancet* 2: 931 (Nov. 1), 1958.

It has been suggested that magnesium may be related to cholesterol metabolism, atherosclerosis, and ischemic heart disease. Accordingly, possible relations between serum magnesium and lipids were investigated in clinically healthy middle-aged American men, a group of men with recent myocardial infarction, and in mothers and their newborn infants. The serum cholesterol levels of

the control group of men varied widely, but there was no correlation between magnesium and cholesterol, total lipid or alpha or beta lipoprotein. The mean cholesterol of 246 mg. per 100 ml. in the infarction group approximated the mean of 237 mg. per 100 ml. in the clinically normal group. The mean serum magnesium level of 1.81 mEq. per liter in the infarction group differed little from that in the healthy group. The mean serum cholesterol of 20 women at term was  $273 \pm 52$  mg. per 100 ml. whereas that of the cord blood was  $82 \pm 17$  mg. per 100 ml. Despite the 4-fold difference in cholesterol, mean serum magnesium levels did not differ significantly.

KURLAND

**Towers, M. K., and Wood, P.: Use of Iproniazid in Ischemic Angina Pectoris.** *Brit. M. J.* 2: 1067 (Nov. 1), 1958.

Iproniazid was used to treat 40 patients with severe angina pectoris. The drug proved to be effective in reducing the severity and frequency of the attacks. It appears to act by blocking pain and not by improving the coronary circulation. There was no evidence that iproniazid influenced the natural history of the disease. The drug probably acts by a selective analgesic action on muscle pain of ischemic origin. However, iproniazid, by blocking the warning pain, may permit the patient undue exertion and run the risk of myocardial infarction. Hence, its use is not recommended in mild angina. It may be used in severe and recurrent angina, especially if anticoagulants are used concurrently. The patient can often be helped over a prolonged ischemic episode. The drug should be withdrawn when the condition improves, because of its side effects and the risk of serious liver damage. The chief side effects noted were attacks of giddiness and pulmonary edema, presumably from fluid retention. Other reported side effects were those referable to central nervous system stimulation, autonomic stimulation, and those referable to antagonism to vitamin B, including peripheral neuropathy. These side effects naturally limited the usefulness of the drug.

KRAUSE

**Goble, A. J., and O'Brien, E. N.: Acute Myocardial Ischemia.** *Lancet* 2: 873 (Oct. 25), 1958.

Serial estimations of the glutamic oxaloacetic transaminase (GOT) activity of plasma were determined in 18 patients with severe episodes of cardiac pain unassociated with clinical and electrocardiographic evidence of recent myocardial infarction. For comparison, serial GOT levels were obtained in 25 normal subjects and 20 patients

with a history of angina pectoris or previous myocardial infarction who were free from pain. In 24 of 25 normal subjects and 20 patients with known ischemic heart disease without pain the maximum GOT was 10 units. Ten patients had isolated attacks of cardiac pain. In 4 the electrocardiogram showed ST-segment depression and T-wave inversion, and in 2 of these there was an abnormal rise in GOT activity. In the other 6 with unchanged electrocardiographic pattern, there was a rise in GOT activity in 2. Eight patients had recurrent attacks of cardiac pain for 2 weeks or more (4 with ST-segment and T-wave changes and 4 with none). In all these patients there were intermittent or irregular rises in GOT to abnormal levels. Thus of 18 patients with long continued typical cardiac pain, there were 12 with increased GOT levels. The attacks were in no way different from those in the patients without ensuing GOT rise. Severity and duration of pain, associated dyspnea, sweating, and temporary fall in blood pressure and electrocardiographic changes were regarded as poor guides to necrosis. New terminology is obviously needed.

KURLAND

**Wenger, N. K., and Bauer, S.: Coronary Embolism. Review of the Literature and Presentation of Fifteen Cases.** *Am. J. Med.* 25: 549 (Oct.), 1958.

Fifteen cases of coronary artery embolism confirmed by postmortem examination were presented with a detailed description of 3. Subacute bacterial endocarditis was the cause of embolism in more than half the cases. Three instances of coronary artery embolism incidental to the cause of death were also reported, 2 secondary to calcified atrial thrombi, and 1 to terminal endocardiosis, suggesting that nonfatal coronary emboli may not be rare. Left coronary artery embolism accounted for 75 per cent of the reported cases. Common clinical manifestations consisted of pain, shock, arrhythmia, and pulmonary edema, but sudden death occurred in 60 per cent of the cases, particularly with involvement of the left coronary artery.

KURLAND

**Caster, W. O., Garamella, J. J., Veloso, A., and Naidu, R.: Effect of Acute Coronary Occlusion upon the Movement of Evans Blue Dye into Different Areas of Pig Heart Muscle.** *Am. Heart J.* 56: 658 (Nov.), 1958.

The hemodynamic changes occurring in different portions of the pig heart following ligation of the left anterior descending coronary artery were studied by the method of determining the Evans-blue space in tissue samples. Ligation of

this artery resulted in a significant decrease in the Evans-blue space in the parts of the myocardium supplied by this artery. The observed Evans-blue space remained substantially constant from 2 to 6 minutes following ligation. The observations were consistent with the suggestion that there was a continued and well-distributed blood flow through a substantial portion of the ischemic areas, but tell nothing about the direction or source of this flow. Quinidine did not affect the Evans-blue space of ischemic or non-ischemic areas, thus indicating that its protective action was related to factors other than increases in blood supply.

SAGALL

**Bruce, R., Todd, J. K., and LeDune, L.: Serum Transaminase: Its Clinical Use in Diagnosis and Prognosis.** *Brit. M. J.* 2: 1125 (Nov. 8), 1958.

The authors cited their experience with serial transaminase determinations in 31 patients with recent myocardial infarction. This report confirmed the value of the test at times before diagnostic electrocardiographic changes appeared. It was suggested that the determination should be obtained at 24-hour intervals from the time of suspected myocardial infarction for at least 4 to 7 days, or until the peak value was passed. Evidence was presented to support the fact that serum glutamic oxaloacetic transaminase levels above 250 units indicated a poor prognosis.

KRAUSE

**Dewar, H. A., Rowell, N. R., and Smith, A. J.: Serum Glutamic Oxaloacetic Transaminase in Acute Myocardial Infarction.** *Brit. M. J.* 2: 1121 (Nov. 8.), 1958.

Serum glutamic oxaloacetic transaminase (SGOT) activity was determined daily for at least 10 days in 34 acute episodes of myocardial infarction in 28 patients. The rise in SGOT was more prompt, more striking, more specific, more sensitive and briefer than either the body temperature or the erythrocyte sedimentation rate. The maximum elevation in SGOT activity roughly correlated with the extent of myocardial damage as estimated by the electrocardiogram. Other conditions can also raise the serum level of SGOT of which the most important is centrilobular necrosis of the liver secondary to heart failure. The average SGOT activity in normal individuals varied from 5 to 40 units per ml. of serum. However, in small infarcts the SGOT may show a characteristic curve although the peak value does not exceed 40 units. Estimation of SGOT is particularly useful (a) when the electrocardiogram shows evidence of previous myocardial infarction.

tion, arrhythmia, bundle-branch block, left ventricular strain, and digitalis effect; (b) when extension of the myocardial infarction is suspected; and (c) to distinguish between acute coronary insufficiency and myocardial infarction. The authors reported, however, that in 8.8 per cent of their patients with recent myocardial infarction, there was no rise in SGOT activity.

KRAUSE

### ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY

#### AND OTHER GRAPHIC TECHNIQS

**Abel, H.: Relation of Cardiac Stroke Volume to the R-R Interval in Complete arrhythmia.**

Ztschr. Kreislaufforsch. 47: 992 (Nov.), 1958.

In an unspecified number of patients with complete arrhythmia due to atrial fibrillation, the ventricular stroke volume (calculated from the displacement ballistocardiogram according to Klensh) increased with the R-R interval of the electrocardiogram. Patients in whom this increase was fairly linear showed fewer signs of cardiac decompensation than those in whom this increase was irregular or showed great scatter.

LEPESCHKIN

**Fiandra, O., Barcia, A., Cortes, R., and Stanham, J.: The Electrocardiographic Pattern of Hypertrophy of the Pulmonary Artery Conus.** Arch. mal. coeur. 51: 858 (Sept.), 1958.

Of 24 patients who showed an rSr' or rSR' pattern in V<sub>1</sub> and a normal QRS duration, hypertrophy of the right ventricle and pulmonary arterial conus was found in 21. Only 3 persons, 7 to 23 years old, were completely normal, and in these persistence of fetal hypertrophy of the conus was assumed. In other patients who had shown conus hypertrophy roentgenologically, the pattern in question was present in high precordial leads although it was absent in V<sub>1</sub>. The authors therefore attributed this pattern to hypertrophy of the pulmonary conus or the outflow tract of the right ventricle, rather than to incomplete right bundle-branch block.

LEPESCHKIN

**Heeger, H., Esch, I., and Saiko, G.: Rheocardiographic evaluation of mitral valvular disease.** Ztschr. Kreislaufforsch. 47: 893 (Oct.), 1958.

The rheocardiogram (electric conductivity curve) in a lead between right shoulder and heart apex was studied in 60 patients with mitral valvular disease. In mitral regurgitation the fall of conductivity at the beginning of systole was

smaller than in normal individuals, probably due to an increase of atrial volume during regurgitation. The systolic rise of conductivity due to aortic filling was smaller, probably because of decreased stroke volume. The metasystolic fall and the diastolic rise of conductivity were steeper, probably because of more rapid ventricular filling. This rise sometimes showed a notch corresponding to the third sound. In mitral stenosis the protosystolic fall was greater and the systolic rise later and smaller; this was attributed to smaller left ventricular filling. The diastolic rise was steeper and showed a sudden slowing at the time of the opening snap of the mitral valve. In some patients the metasystolic dip was very shallow; this was attributed to a high peripheral arterial resistance, because this dip became deeper and steeper after this resistance was decreased by Regitine.

LEPESCHKIN

**Portheine, H.: Vectorcardiographic Studies in Myocardial Infarction in the Posterior Wall of the Heart.** Arch. Kreislaufforsch. 29: 31 (Sept.), 1958.

Cube system vectorcardiograms of 125 patients with posterior myocardial infarction showed in most instances a smooth Q portion of the QRS loop, directed upward, anteriorly, and to the left, without significant changes in the R and S portions. This pattern corresponds to diaphragmatic location of the infarction. In a smaller group of patients, usually showing a posterolateral location of the infarction, an indentation was found on the boundary between the R and S portions of the loop. In these patients the standard electrocardiogram may show only very low voltage of the R wave leads II and V<sub>6</sub>. A combination of both patterns usually indicated extensive posterior infarction. In the healing phase the T loop was usually deviated upward, anteriorly, and to the left.

LEPESCHKIN

**Abel, H., and Mühler, E.: Myocardiosis and the Ventricular Gradient.** Ztschr. Kreislaufforsch. 47: 887 (Oct.), 1958.

In 6 patients with hepatic cirrhosis or hepatitis the ventricular gradient and the area vector of T were abnormally low but the area vector of QRS was unchanged. Progression of hepatic damage was usually accompanied by further decrease of the gradient, but in some cases the latter became temporarily normal. The changes are attributed to a "myocardiosis" resulting from an abnormal myocardial metabolism.

LEPESCHKIN

**Söderström, N.: The Diagnosis of Partial Atrio-Ventricular Block and Adams-Stokes Syndrome in Patients with Auricular Fibrillation.** *Cardiologia* 33: 397, 1958.

In the presence of atrial fibrillation, complete atrioventricular (A-V) block is not difficult to recognize but according to the author, conventional criteria do not permit a reliable diagnosis of *partial* (intermittent) A-V block. A method is described for the detection of such a block in atrial fibrillation by measuring a sufficient number of R-R intervals. In such tracings, partial A-V block is indicated by the presence of *equal* R-R intervals which are longer than most other R-R intervals in that particular case. The duration of these equal intervals is usually of the order of 1.30 to 1.80 sec. Intervals of this type should be regarded as expressions of ventricular escape. The presence of still longer R-R intervals indicates an insufficiency of the escape mechanism and an immediate danger of Stokes-Adams episodes.

BRACHFELD

**Heinecker, R., and Zipf, K. E.: The Concept of "Intrinsic Deflection" in the Presence of Notched R-Waves.** *Cardiologia* 33: 407, 1958.

The concept of "intrinsic deflection" is briefly reviewed and the applicability of the terms "onset of maximum negative deflection" to R waves and "upper turning point" with more than 1 peak is examined. In some cases with conduction disturbances clearly indicated in the limb leads these terms were found inadequate when applied to the chest leads. In these cases, the "onset of the last negative deflection" was always delayed so that the use of this last item is recommended.

BRACHFELD

**Medrano, G. A., Sodi-Pallares, D., Marisco, F., and Bisteni, A.: The Importance of Septal Activation in the Electrogenesis of the Unipolar Morphologies in Bundle Branch Block: Experimental Study with Total Extirpation of the Free Ventricular Wall of the Blocked Ventricle.** *Am. Heart J.* 57: 126 (Jan.), 1959.

To investigate the hypothesis that the bizarre QRS complexes seen in bundle-branch block result primarily from slow activation in the free ventricular wall of the blocked ventricle, the authors produced bundle-branch block in dogs and then completely extirpated the free ventricular wall of the blocked ventricle. Electrocardiographic studies showed no alteration in the general morphology of the tracings following this procedure. These experiments indicate that in bundle-branch block the free ventricular wall of

the blocked ventricle contributes only poorly to the formation of the QRS complexes and that the forces of septal activation are the most important factor in their genesis.

SAGALL

**Minhas, K., and Gasul, B. M.: Systolic Clicks: A Clinical Phonocardiographic, and Hemodynamic Evaluation.** *Am. Heart J.* 57: 49 (Jan.), 1959.

In a study of 809 phonocardiographic tracings on a total of 598 patients early systolic clicks or ejection sounds were found in 135 and mid or late systolic clicks in 11. The systolic clicks detected in mid and late systole occurred mostly in normal individuals and were thought to be of no significant diagnostic importance, whereas the early systolic clicks were found almost exclusively with abnormal hearts. These early systolic clicks were observed in congenital anomalies producing stenosis of the aortic and pulmonary valves and in those involving dilatation of the aorta and pulmonary artery. The aortic clicks were of maximal intensity at the apex and showed only slight variation with respiration, whereas the pulmonic clicks were loudest at the second left intercostal space parasternally and were intensified by expiration. The early systolic clicks were considered to be a pathologic manifestation of the second major or ejection component of the first heart sound and, depending on their origin, to reflect the isometric contraction period or beginning of the ejection phase of either ventricle. In congenital aortic stenosis and valvular pulmonary stenosis the early systolic clicks seemed to originate at the valvular level just after the atrioventricular closure while in other conditions they seemed to originate in the vessel wall of the aorta or pulmonary artery. Although early systolic clicks are considered to be abnormal findings of significant diagnostic importance, their absence does not exclude any specific entity or hemodynamic abnormality.

SAGALL

**Dower, G. E., and Osborne, J. A.: Surface Activation of Guinea Pig Ventricles Determined by Intracellular Electrodes.** *Am. J. Physiol.* 195: 396 (Nov.), 1958.

Intracellular micro-electrodes were used to record the arrival of the activation process in myocardial fibers of the intact ventricle of the guinea pig. Arrival of excitation was indicated by the steepest part of the upstroke of the transmembrane action-potential curve obtained. The times of arrival of the activation process at various points on the surface of the ventricles were measured with respect to selected points on a simul-

taneous electrocardiogram that served as a standard of reference. Measurement of these relative activation times indicated that the right ventricle tended to be activated earlier than the left ventricle, except on their dorsal surfaces, where there was little difference. Three different types of upstrokes were recorded in the monophasic records obtained with intracellular electrodes. The association between relative activation time of a region and the type of upstroke is explained by the position of the recording electrode relative to the stimulus.

KAYDEN

### ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Jannach, J. R.: Myocarditis in Infancy with Inclusions Characteristic of Psittacosis. *J. Dis. Child.* 96: 734 (Dec.), 1958.

An 18-month-old child with myocarditis due to a psittacosis agent is reported. Clinical laboratory, and necropsy findings are carefully and thoroughly recorded. The literature concerned with myocarditis in infancy is reviewed and the author emphasizes that the sudden onset of heart failure with cardiac enlargement and nonspecific electrocardiographic changes in a child under 2 years of age is most suspicious of myocarditis.

KARPMAN

Szakács, J. E., and Cannon, A.: L-Norepinephrine Myocarditis. *Am. J. Clin. Path.* 30: 425 (Nov.), 1958.

The myocardial lesions caused by l-norepinephrine were found in autopsied patients who had been treated with l-norepinephrine infusions, from autopsied material of pheochromocytoma and from autopsied dogs who had been infused with l-norepinephrine. Two patients were briefly presented who had been treated with l-norepinephrine. Microscopic examinations of the heart showed focal myocarditis in both cases. There was edema, degeneration of myofibrils, and focal pleomorphic infiltrations by leukocytes. Of 17 adults dying with pheochromocytoma, acute myocarditis was found in 3 patients. The continuous infusion of l-norepinephrine to 8 dogs over a period of 107 to 397 hours was carried out at varied rates of infusions. In 4 animals the rate of infusion was 0.8 to 0.9  $\mu\text{g./min./Kg.}$  There were no gross pathologic changes noted at autopsy. In 4 other animals, the rate of infusion was maintained at 2.2  $\mu\text{g./min./Kg.}$  for most of the experimental period. Gross pathologic findings included large subendocardial and myocardial

hemorrhages in both ventricles, the right atrial wall, and the mitral valve. Pericardial examination showed subepicardial hemorrhages and pericardial hemorrhage without effusion. Hemorrhages were also noted in stomach, duodenum, retroperitoneal structures, and beneath the renal capsule. Microscopic examination of the heart revealed both endocardial and myocardial lesions. In the endocardium, proliferation, edema, and thickening accompanied the hemorrhages. Myocardial lesions showed edema, degenerating myofibrils, and cellular infiltration. Degenerative changes and in extreme cases necrotic changes were noted in arterial and arteriolar walls.

KAYDEN

### HYPERTENSION

Hudson, A. J., and Hyland, H. H.: Hypertensive Cerebrovascular Disease: A Clinical and Pathologic Review of 100 Cases. *Am. Int. Med.* 49: 1049 (Nov.), 1958.

The 100 patients chosen for this study had indisputable evidence of hypertension and a detailed autopsy examination. The average duration of hypertension was 7 1/4 years, and the average blood pressure recording for the entire series was approximately 220/126 mm. Hg. The cerebrovascular accidents were considered as due either to vascular insufficiency or occlusion or to hemorrhage. At autopsy eighty-five per cent of the series had cerebral lesions due to hemorrhage or softening. There was no history or clinical finding of any neurologic difficulty in one quarter of these cases. Forty-seven per cent of the series had a history of strokes, thought to be due to vascular insufficiency or occlusion. In 31 per cent of the series, death was due to a large intracranial hemorrhage. The principal sites of hemorrhage in the fatal cases were the cerebrum (74 per cent), the pons (23 per cent), and the cerebellum (3 per cent). In 10 per cent of the whole series, an intracerebral hemorrhage of moderate size was found but was not the cause of death. In an additional one quarter of the patients, minute, often multiple and usually asymptomatic, hemorrhages were found at autopsy. In only 1 patient was an unequivocal diagnosis of hypertensive encephalopathy made. Severe mental deterioration was found in 18 per cent of this series. About four fifths of the patients had had fundoscopic examination. Venous nicking, arteriolar spasm, right-angle crossing of arterioles by veins, and silver-wire effect were noted in 87 per cent. Two thirds of the patients examined showed retinal hemorrhage and a little more than one half of those examined had papilledema. The authors doubt that papilledema is a result of cerebral

edema but suggest that it is more likely due to vascular changes in the ocular fundus that produce local ischemia and edema of the retina and optic disk.

KAYDEN

**Sturtevant, F. M.: Effect of Sodium Intake Level on Hypertensive Disease in Rats.** *Am. J. Physiol.* 195: 85 (Oct.), 1958.

Hypertension was induced in 30-day old rats by the subcutaneous implantation of a wax pellet containing 20 mg. of desoxy corticosterone acetate. Normal saline ad libitum was offered as the sole drinking fluid. At 18 weeks of age, the group was divided into a water group, which received tap water for drinking, and a saline group, which continued on normal saline throughout the experiment. The median survival for the 2 groups and the blood pressure of the 2 groups showed no statistical difference over a period of 44 weeks. When the tap water group was offered only saline 1 day a month, the rats tended, on the average, to have lower intakes and outputs of sodium and water than the rats accustomed to saline.

KAYDEN

**Bär, C. G., and Bachmann, K.: Phases of Cardiac Contraction in Hypertension.** *Cardiologia* 33: 434, 1958.

In 45 normotensive and 59 hypertensive subjects, circulatory dynamics were analyzed by means of simultaneous recording of the electrocardiogram, phonocardiogram, and the carotid and femoral pulses. In the hypertensive patients without cardiac failure normal values were found for the isometric contraction and ejection phases. The data did not make possible any assessment of increased efficiency of cardiac contraction during reduction of the blood pressure in hypertensive patients. Incipient or manifest left ventricular failure could not be recognized with certainty from the determination of the isometric contraction and ejection phases.

BRACHFELD

**Schmitt, H., and Schmitt, H.: A Study of the Mechanisms of Hypotension Produced by Reserpine and by Rescinamine.** *Arch. int. Pharmacodyn.* 117: 374 (Nov.-Dec.), 1958.

The hypotensive effects of reserpine and rescinamine were investigated in the dog, rabbit and monkey. The fall in peripheral resistance produced by these drugs was found to be central in origin, yet it was not the result of any direct action on nervous centers. Certain inhibitory mechanisms were found to be increased such as

electric excitability of the nerves of Hering and Ludwig-Cyon and the action of veratrine. The hypothesis of a decrease in the level of norepinephrine in the postganglionic fibers after the injection of reserpine fits most of the authors' experimental results.

BRACHFELD

**Nussbaum, H. E., Leff, W. A., Mattia, V. D., and Hillman, E.: Fixed Combination of Chlorothiazide-Reserpine in Hypertension.** *Am. J. M. Sc.* 236: 786 (Dec.), 1958.

Twenty-eight patients with essential hypertension and 1 with chronic glomerulonephritis were provided with tablets containing 500 mg. of chlorothiazide and 0.125 mg. of reserpine. The dosage varied from patient to patient but the average was 1 tablet twice a day. In addition, most of the patients had been receiving a ganglion-blocking agent, either alone or with reserpine, digitalis and an oral mercurial diuretic. Blood pressure was checked in both the supine and upright positions. Using a reduction in the mean blood pressure of 20 mm. Hg or more, or a return to normotensive levels as the criterion for response, the over-all response rate to combination therapy of chlorothiazide and reserpine was 54 per cent. The results were not so good as the 70 to 75 per cent response rate previously observed with mecamylamine in the same group of patients. However, during the course of therapy with chlorothiazide alone only 12 out of 129 patients showed a significant response. In no instance was there a serious drop in serum levels of sodium, potassium, and chloride. There were no specific electrocardiographic changes. No significant side effects were observed. The authors conclude that chlorothiazide is a useful drug when used in combination with other hypertensive agents. They suggest that its effects may be due in part to a direct hypertensive action and in addition the apparent potentiating effect may be due to a delay in excretion of the other hypertensive agents being administered at the same time.

SHEPS

**Silva, T. F., and Sommers, S. C.: Renal Biopsy Changes with Pheochromocytoma.** *Am. J. M. Sc.* 236: 700 (Dec.), 1958.

Renal tissue obtained by biopsy in 9 patients who subsequently underwent removal of a pheochromocytoma was reviewed. The most striking alteration consisted of muscular hypertrophy and secondary degenerative changes in the renal arteries and large arterioles. The smaller arterioles

were relatively less narrowed by muscular spasm and hypertrophy. Larger renal veins were quite congested. This situation is a reverse of that found in essential hypertension in which small renal arterioles are the most thickened and in which arteries and large arterioles may at first appear dilated and only subsequently become hypertrophied. In contrast to the glomerular ischemia characteristic of the established essential hypertension, in hypertension accompanying pheochromocytoma there is glomerular hyperemia with an unusual local dilatation of capillaries either at the glomerular root or in the peripheral loops. The dilatation of the root capillaries resembles the jet effect of blood released rather abruptly from the concentrically hypertrophied, narrowed afferent arterioles usually present. In 1 patient who had a renal biopsy at the time of a bilateral lumbar sympathectomy and in whom hypertension persisted for 8 years prior to removal of the pheochromocytoma, the second renal biopsy revealed a progression of renal arteriolar thickening and fibrous replacement of smooth muscle and in addition, glomerular ischemia with atrophy and thickening of the basement membrane. These changes were irreversible in contrast to the muscular hypertrophy and edema seen in the earlier cases. In contrast there was a second patient who had a pheochromocytoma removed and was normotensive for 6 years prior to a second kidney biopsy. The focal abnormalities of the arteriolar and glomerular capillary walls persisted but without any evident permanent significant narrowing either of arterioles or capillaries. There were no clinical pathologic distinctions found between the kidney changes that accompanied the tumors that secreted mostly epinephrine and the tumors that produced more norepinephrine.

SHEPS

**Gross, F., and Lichtlen, P.: Experimental Renin Content of Kidneys in Intact and Adrenalectomized Rats Given Cortexone.** *Am. J. Physiol.* 195: 543 (Dec.), 1958.

The hypertension that develops in rats after unilateral renal ischemia is decreased after adrenalectomy and the content of pressor substance in the unchanged kidney is restored when the animals are kept alive by maintenance doses of cortisol. The same results were noted when a maintenance dose of cortexone (desoxycorticosterone) was used instead of cortisol. The subcutaneous implant of a large excess of cortexone restored the hypertensive response to renal ischemia despite adrenalectomy. Measurement of the content of pressor material revealed a normal

amount in the clamped kidney and a decreased amount in the contralateral kidney. This difference was absent after adrenalectomy if small doses of cortexone were used but was evident in the presence of excess cortexone. Cortexone given in high dosage to intact animals produced a diminution of pressor substance in the kidneys but no significant elevation of blood pressure. Cortexone given in high dosage to animals with 1 kidney artery clamped resulted in normal concentration of pressor substance in the clamped kidney but a complete disappearance of this substance from the unclamped kidney. Clamping of the renal artery appeared to be a maximal stimulus for hypertension and for changes in content of renal pressor substance and no accentuation occurred when high doses of cortexone were added.

KAYDEN

**Lee, R. E., Seligmann, A. W., Clark, M. A., Borhani, N. O., Queenan, J. T., and O'Brien M. E: Therapeutically "Refractory" Hypertension: Causative Factors, and Medical Management with Chlorothiazide and Other Agents.** *Ann. Int. Med.* 49: 1129 (Nov.), 1958.

A group of 35 patients with hypertension had shown unsatisfactory responses to reserpine (9 patients), reserpine and hydralazine (21 patients), and "autonomic blocking" drugs plus reserpine and hydralazine (5 patients). Failure of these agents was most often due to their undesirable side effects. Chlorothiazide was added in doses of 250 mg. 4 times a day or 500 mg. twice daily. In a majority of patients, there was an impressive reduction in the blood pressure after a period of 6 to 7 days of treatment. Seven patients whose blood pressure had not fallen even while on high doses of previous medications, showed acceptable blood pressure reductions when chlorothiazide was added to their medications. There appeared to be no close correlation between the diuretic response and the hypotensive effect. Three patients did not respond even to the addition of chlorothiazide to the treatment schedule. Side effects of chlorothiazide medication included gastrointestinal complaints of nausea, epigastric distress, abdominal cramps and vomiting in 7 cases. Cardiac irregularities were produced in 4 patients who were on digitalis, possibly due to potassium loss. One patient developed gross hematuria and petechiae after receiving chlorothiazide for 8 days. In 1 patient with epilepsy, an increased number of seizures occurred during chlorothiazide medication, possibly due to hypochloremic alkalosis.

KAYDEN

**Billow, B. W.:** Effect of a New *Rauwolfia* Derivative, Deserpidine, in Hypertension. New York State J. Med. 58: 3641 (Nov.), 1958.

Deserpidine is an alkaloid from *Rauwolfia canescens*. The authors reported their experiences over a 1 year period with the use of deserpidine in 93 patients with hypertension. Seventy-five patients had mild, 10 had moderately severe, and 8 had malignant hypertension. Deserpidine was found to be effective as a mild hypotensive agent with minimal side effects. The results in the 75 mild hypertensive patients were qualitatively similar to those seen with reserpine in similar dosage ranges. The initial average dosage was 0.1 to 0.25 mg. 3 or 4 times daily. No patient received more than 6 mg. daily in this study. Deserpidine produced no reduction in blood pressure among 18 moderately severe and malignant hypertensive patients, although its administration resulted in symptomatic improvement. Toxic reactions were exceedingly mild, none severe enough to interrupt therapy. However, side effects such as nausea, lethargy, depression, and nasal congestion did occur. Laboratory studies during medication revealed no blood or urinary abnormalities or evidence of hepatic or renal damage.

KRAUSE

#### METABOLIC EFFECTS ON CIRCULATION

**Berteau, B. A., Engstrom, W. W., and Engbring, N. E.:** Cardiac Complications in Patients with Nontoxic and Toxic Nodular Goiter and with Graves' Disease. J. Lab. & Clin. Med. 65: 687 (Nov.), 1958.

The group of patients studied included patients with Graves' disease who had a much lower average age than those with nodular goiter, uncommonly had atrial fibrillation, organic heart disease, and heart failure; whereas those with toxic nodular goiter had a higher frequency of cardiac arrhythmia, organic heart disease, and heart failure. Most of the arrhythmias were chronic atrial fibrillation, although some had paroxysmal arrhythmias. Patients with nontoxic goiter had a lower incidence of arrhythmias, organic heart disease, and heart failure than those with toxic nodular goiters, although the ages were comparable. It was concluded that in elderly patients with nodular goiters atrial fibrillation pointed with certainty to independent organic heart disease. No difference in the level of the circulating thyroid hormone could be demonstrated between those patients with fibrillation and those in sinus rhythm. Adequate treatment of the thyrotoxicosis of nodular goiter was associated with the spontaneous return to sinus rhythm in a fourth of the patients

with cardiac arrhythmia. Considerable improvement in heart failure was the most consistent finding when hyperthyroidism was controlled. In those patients with toxic nodular goiter, even with sinus rhythm, the diagnosis of organic heart disease and heart failure was more frequent than with the nontoxic group of a similar age, indicating that thyrotoxicosis exerted a deleterious effect on the heart.

MAXWELL

**Furchgott, R. F., and De Gubareff, T.:** The High Energy Phosphate Content of Cardiac Muscle under Various Experimental Conditions Which Alter Contractile Strength. J. Pharmacol. & Exper. Therap. 124: 203 (Nov.), 1958.

Marked changes in contractile strength of cardiac muscle may be produced by a variety of agents and conditions independent of any changes in the concentrations of high energy phosphate compounds. This conclusion was based on determinations made of the concentrations of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenylic acid, creatine phosphate (CP), and inorganic phosphate in isolated, electrically driven left atria of guinea pigs. In hypodynamic atria, which had undergone spontaneous failure, the mean concentrations of the high energy phosphate compounds ATP, ADP, and CP were not significantly different from the respective mean concentrations in control atria prior to failure, or from those concentrations in atria that had been restored from failure with strophanthin-K. Decreases in contractile strength resulting from a reduction in frequency of stimulation, addition of acetylcholine, or addition of ryanodine were not associated with significant changes in concentrations of high-energy phosphate compounds from the control levels. Increases in contractile strength resulting from the addition of nontoxic doses of strophanthin-K, of extra calcium chloride or of epinephrine in a final concentration around  $10^{-7}$ , were not associated with any significant changes in concentrations of high-energy phosphate compounds from the control levels. Anoxia produced a marked decrease in both contractile strength and high-energy phosphate content, with the fall of CP being much greater than that of ATP. Poisoning with excess glycoside also produced both a decrease in contractile strength and a decrease in CP and ATP. Moderate decreases in these compounds also occurred in atria exposed to a low potassium medium, even though this procedure led to an increase in contractile strength. Epinephrine and norepinephrine in concentrations giving maximal stimulation of contractile strength  $10^{-6}$  to  $10^{-5}$  produced small but significant decrease in CP.

RINZLER

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## AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

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### APPLICATIONS FOR AHA RESEARCH SUPPORT NOW BEING INVITED

The Association is now accepting applications from research investigators for support of studies to be conducted during the fiscal year beginning July 1, 1960.

September 15, 1959, has been set as the deadline for applying for research fellowships and established investigatorships. Applications for grants-in-aid must be made by November 1, 1959.

Applications may be made for awards in the following categories:

*Established Investigatorships:* Usually awarded for five years, subject to annual review, in amounts ranging from \$6,500 to \$8,500 yearly plus dependency allowance, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. In addition, a grant of \$500 is made to the investigator's department to assist in defraying the expenses of his research program. Applicants for Established Investigatorships may apply for grants-in-aid to support their research at the same time they apply for Established Investigatorships.

*Advanced Research Fellowships:* Awarded for periods of one or two years to postdoctoral applicants who have had some research training and experience but who are not clearly qualified to conduct their own independent research. During the second year of tenure they will be permitted to spend up to 25 per cent of their time in professional and scientific activities not strictly of a research nature, providing that these will contribute to their professional development and

do not involve services for a fee. These stipends range from \$4,600 to \$6,500 annually. Additionally, a grant of \$500 is made to the investigator's department, as in the case of Established Investigators.

*Research Fellowships:* A limited number of awards are available to young men and women with doctoral degrees for periods of one or two years to enable them to train as investigators under experienced supervision. Annual stipends range from \$3,800 to \$5,700. However, this type of award is primarily made by local Heart Associations.

*Grants-in-Aid:* Made to experienced investigators to help underwrite the costs of specified projects, such as equipment, technical assistance and supplies.

The Association also maintains another form of research support, the *Career Investigatorship*. This is given to a limited number of scientific investigators of unusual capacity and widely recognized accomplishment to assure them of financial support throughout their productive lives. Career Investigators are selected on the initiative of the Research Committee of the Association and *not by application*.

At least half of all funds received by the American Heart Association's National Office are allocated for research. Since its reorganization as a national voluntary health agency in 1948, the Association and its affiliates and chapters have allocated more than \$40,000,000 to scientific research.

Further information and application forms may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N.Y.

### RECOMMEND EARLY REGISTRATION FOR AHA SCIENTIFIC SESSIONS

Early registration is recommended for those planning to attend the 32nd annual Scientific Sessions of the American Heart Association at the Trade and Convention Center in Philadelphia, October 23-25. Physicians who register by mail will receive a complimentary advance copy of the program booklet containing abstracts of the proceedings, which will sell for \$2.00 at the meeting. Forms for registering and for reserving accommodations are now available from the Association.

This year for the first time the American College of Cardiology will hold its Interim Meeting concurrently with the Heart Association's Scientific Sessions. On Friday, October 23, the College will hold a dinner to be followed by "Fireside Conferences" to which Heart Association members are invited. A panel on "Cardiac Resuscitation" will be presented jointly by the College and the AHA Council on Clinical Cardiology on Sunday Afternoon.

The Association's Council on Arteriosclerosis, formerly the American Society for the Study of Arteriosclerosis, will present a symposium and a scientific session as part of the AHA scientific program. The new Council will hold its business and independent scientific meeting in Chicago, November 8-9.

Following is a tentative outline of the AHA Scientific Sessions program:

#### Friday, October 23:

A morning session on clinical cardiology will be devoted to a symposium on "Regulatory Mechanisms of the Cardiovascular System." Simultaneous morning sessions are scheduled on the subjects of rheumatic fever and congenital heart disease, and on circulation. The afternoon program includes: presentation of submitted papers of general interest in clinical cardiology; the Lewis A. Conner Memorial Lecture, to be given by Louis N. Katz, M.D., Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago; and a session on cardiovascular surgery.

#### Saturday, October 24:

A morning session on clinical cardiology will consist of two symposia: "Recent Developments in Diagnostic Techniques" and "Open Heart Surgery in Acquired Valvular Disease." Concurrently, a morning session will be held on high blood pressure research. Scheduled during the afternoon are: presentation of the Albert Lasker Award; the George E. Brown Memorial Lecture, by Ludwig W. Eichna, M.D., Professor of Medicine, New York University College of Medicine; a symposium on "Congestive Heart Failure," including a panel on "Treatment of Congestive Heart Failure" and a presentation on "Life After Heart Failure"; a session on basic science; and a session on cardiovascular surgery.

#### Sunday, October 25:

Included in the morning sessions are a panel on "Conflicting Concepts of Atherogenesis" and a concurrent session on "Instrumental Methods in Cardiovascular Research." In addition to a panel to be conducted jointly with the American College of Cardiology during the afternoon, a concurrent session will be devoted to arteriosclerosis.

#### Deadline for Abstracts is June 12

June 12 is the deadline for submitting abstracts of papers to be presented at the Scientific Sessions. Applications for space for scientific or industrial exhibits also must be submitted by June 12.

### EDUCATIONAL PROGRAM PLANNED ON CONGESTIVE HEART FAILURE

A special educational program on the subject of congestive heart failure, to be directed initially to members of the medical and allied professions, has been developed by the American Heart Association. Programs will be subsequently developed for public education and community services in this field.

Plans for the professional program include the publication of a series of articles on congestive heart failure in *Circulation*, beginning with the January, 1960 issue. The sub-

ject will also be given prominence in two issues of *Modern Concepts of Cardiovascular Disease*. In addition, the entire January-February issue of *The Heart Bulletin* will be devoted to it.

Medical societies will also be encouraged to present special programs on congestive heart failure and efforts will be made by AHA affiliates and chapters to emphasize the subject in all media of professional communication, at meetings attended by physicians and at post-graduate courses.

### NEW CAREER INVESTIGATOR APPOINTED BY ASSOCIATION

Donald B. Zilversmit, Ph.D., Professor of Physiology, University of Tennessee, Memphis, has been appointed as a Career Investigator of the American Heart Association. This brings to seven the number of scientists whose research is being supported on a lifetime basis by the Association and its affiliates.

Dr. Zilversmit, who came to the United States shortly before World War II, received B.S. and Ph.D. degrees from the University of California. In 1948, he went to the University of Tennessee as an instructor in Physiology, progressing to the rank of full professor in 1956. Until recently, he was a member of the Metabolism and Nutrition Study Section of the National Institutes of Health and will be Chairman of the 1959 Gordon Conference on Lipid Metabolism. He is a member of the Executive Committee of the AHA Council on Arteriosclerosis.

In his studies, the 39-year-old Dutch-born Dr. Zilversmit has concentrated on the body's use of lipids found in the blood and in atherosclerotic patches in the arteries. He has also made a major contribution to the use of radioactive tracers in measuring animal and human use of lipids. As an outgrowth of his interest in radioactive isotope methods, Dr. Zilversmit was able to suggest a technique in orthopedic surgery for gaging the state of the blood supply by inserting a Geiger counter in bone using radioactive phosphorous as a tracer. More recently, Dr. Zilversmit and

his associates have developed an artificial fat emulsion suitable for injection as a nutrient for certain patients.

Previously appointed as AHA Career Investigators are Victor Lorber, M.D., Professor of Physiology, and Lewis W. Wannamaker, M.D., Associate Professor of Pediatrics, both of the University of Minnesota; John R. Pappenheimer, Ph.D., Visiting Professor of Physiology, and Albert H. Coons, M.D., Visiting Professor of Bacteriology and Biochemistry, both of Harvard Medical School; David B. Sprinson, Ph.D., Professor of Biochemistry, and John V. Taggart, M.D., Professor of Medicine, both of Columbia University College of Physicians and Surgeons.

The Career Investigatorship, pioneered by the Association in 1951, provides \$30,000 annually not only to cover the recipient's stipend but also his laboratory expenses. Its purpose is to relieve leading investigators of financial and other pressures and permit them to work without interruption on problems of their own choosing.

### SWEDISH PEDIATRICIAN TO ADDRESS SEMINAR

John Lind, M.D., Head of the Department of Pediatrics, Caroline Hospital, Stockholm, Sweden, will be guest speaker at a seminar on Pediatric Cardiology sponsored by the University of California School of Medicine, August 16-19. Further information may be obtained from the Department of Continuing Education in Medicine, UCLA Medical Center, Los Angeles 24, Calif.

### MEETINGS CALENDAR

June 8-12: American Medical Association, Atlantic City. F. J. L. Blasingame, 535 N. Dearborn Street, Chicago 10, Ill.

August 10-13: National Medical Association, Detroit. John T. Givens, 1108 Church Street, Norfolk, Va.

September 13-17: International College of Surgeons, U.S. Section, Chicago. Ross T. McIntyre, 1516 Lake Shore Drive, Chicago 10, Ill.

September 22-25: American Roentgen Ray Society, Cincinnati. C. A. Good, 200 First Street, S.W., Rochester, Minn.

September 28-October 2: American College of Surgeons, Atlantic City. Paul R. Hawley, 40 E. Erie Street, Chicago 11, Ill.

October 19-23: American Public Health Association, Atlantic City. B. F. Mattison, 1790 Broadway, New York 19, N.Y.

**October 23-27: American Heart Association Annual Meeting and Scientific Sessions, Philadelphia. American Heart Association, 44 East 23rd Street, New York 10, N.Y.**

November 2-4: Association of American Medical Colleges, Chicago. Ward Darley, 2530 Ridge Avenue, Evanston, Ill.

November 6-7: Central Society for Clinical Research, Chicago. A. S. Weisberger, 2065 Adelbert Road, Cleveland 6, Ohio.

**November 8-9: American Heart Association's Council on Arteriosclerosis, Chicago. Aaron**

**Kellner, N.Y. Hospital, 525 E. 68th Street, New York 21, N.Y.**

#### ABROAD

June 24-27: 2nd International Conference on Medical Electronics, Paris, France. F. S. Brackett, National Institutes of Health, Bethesda 14, Md.

July 23-30: International Congress of Radiology, Munich, Germany. H. V. Braunbehrens, Ziemsenstr. 1, Munich 15, Germany.

July 27-30: Shaio Foundation Symposium on Cardiovascular Diseases, Bogota, Colombia. Alberto Vejarano-Laverde, 43-23 Carrera 13, Bogota, Colombia.

September 18-20: International Cardiovascular Society, Munich, Germany. H. Haimovici, 715 Park Avenue, New York 21, N.Y.

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